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Increasing Promiscuity and Abuse with the Barbiturates. By J. M. Maas, M.D. 121

The Effects of Intravenous Protoveratrine on Hemodynamics and Exercise Tolerance In Patients with Hypertension. By Frank W. Lovejoy, Jr., M.D., Paul N. G. Yu, M.D., Robert A. Bruce, M.D., Robert E. Nye, M.D., George Welch, M.D., Bernard B. Brody, and John Muxworthy. 129

Treatment of Thyrotoxicosis with Methimazole. By Nelson Taylor, M.D., Myer Teitelbaum, M.D., and Alfred Large, M.D. 138

Localized Myxedema in Relation to Thyrotoxicosis and Exophthalmos. By Serge E. Grynkewich, M.D., Robert M. Laughlin, M.D., Frank T. Herron, M.D., and Willard J. Carmel, Jr., M.D. 142

Re-Feeding (Nutritional) Gynecomastia in Cirrhosis of the Liver: I. Clinical Observations. By Robert M. Kark, M.R.C.P. (Lond.), F.A.C.P., Gordon R. Morey, M.D., and Camen R. Paynter, M.D. 154

Pulmonary Circulation Times with Particular Relationship to Acute Hypoxia. By Howard R. Bierman, M.D. 162

Typhoid Fever of Short Duration. By Franz K. Bauer, M.D., and Albert G. Bower, M.D. 174

NPH Insulin in Diabetic Patients with Complications. By Charles R. Shuman, M.D., and Robert B. Francis, M.D. 179

Serum Complement in Rheumatoid Arthritis. By John H. Vaughan, M.D., Theodore B. Bayles, M.D., and Cutting B. Favour, M.D. 186

The Use of a Cation Exchange Resin in the Management of the Fluid Retentions of Normal and Toxemic Pregnancies. By W. Robert Penman, M.D. 193

Pulmonary Infarction: A Frequently Missed Diagnosis. By Rutledge Miller, and James B. Berry, M.D. 197

Evaluation of a Simplified Thromboplastin Extract. By Fred J. Schilling, M.D., Albert DeNatale, Ph.C., and Frances C. Mottram, B.S. 207

Progress of Medical Science

Surgery—An Inquiry into the Surgical Treatment of Ulcerative Colitis. By Gaylord S. Bates, M.D. 211

Ophthalmology—Ocular Phakomatoses. By Thomas J. Kirby, M.D. 227

Complete contents on adv. page 10

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

AUGUST, 1951

ORIGINAL ARTICLES

INCREASING PROMISCUITY AND ABUSE WITH THE BARBITURATES

By J. M. Maas, M.D.

(From the Lilly Research Laboratories, Indianapolis, Indiana)

A problem of considerable magnitude and with almost endless ramifications confronts almost every thinking and conscientious physician today. This problem concerns the insidious hazards attending the promiscuous use of barbiturates. Hambourger[6] drew attention to the seriousness of the problem in 1940. It has multiplied alarmingly since Robinson[15] and more recently Isbell[7] have expressed the opinion that true addiction follows the use of large doses of the barbiturates over long periods of time. Tatum[19], contrariwise, has stated that habituation rather than addiction takes place under the circumstances cited. The author is inclined to share the latter views.

Lay publications, especially the tabloid type, carry at periodic intervals lurid tales of the havoc wrought by so-called "Devil's Capsules." In these articles, "innocent victims" are portrayed as falling under the ghastly influence of their potential enslaving properties. While it is admittedly true that innocently acquired habituation to the barbiturates does exist in some cases, there is, as will appear, ample evidence that in many instances the habit is brought about by a number of extraneous factors. These include improper methods of distribution of these drugs, the search on the part of individuals to find an escape mechanism from realities, and the utilization of these agents to compensate for the accelerated pace of living so prevalent today.

Attempts at Restriction. Well-meaning legislators have proposed laws to curb the sale of these agents except under conditions provided by the Harrison Narcotic Act. Such action would probably not materially reduce the quantity of barbiturates legitimately prescribed and employed. Conceivably, such laws might be instrumental in providing better distribution of these drugs. However, when one reflects how the narcotic laws are violated and with what ease the barbiturates can be prepared, it behooves one to venture the opinion that such legislation might fail.

Combination with an Emetic. Interested groups have suggested the addition of minute quantities of an emetic drug such as ipecac to every barbiturate formula. Indeed, such combinations are offered to the profession through legitimate channels by at least one ethical pharmaceutical house. The rationale for such a preparation is based on the conjecture that if excessive amounts of the combination are

ingested, an emetic action will ensue, thus causing the hypnotic to be expelled. While in theory this appears to be a practical approach to a serious problem, a number of factors would appear to restrict sharply the successful application of such a compound. The Food and Drug Administration, Federal Security Agency[1], has conducted a research program which has revealed that when such combinations are ingested, the barbiturate is absorbed in sufficiently large quantities to cause death before the emetic component can act. Furthermore, the possibility of chronic ipecac poisoning is alluded to if the barbiturate–emetic combination is ingested each day. However, Miskimon[12] has stated, following a study in dogs, that small doses of an emetic were well tolerated in the presence of a barbiturate within the sedative dose range. When lethel doses of the same barbiturate were administered with proportionately larger quantities of the emetic, emesis ensued. One should, however, bear in mind the species difference and the fact that the emetic center in dogs is readily stimulated.

Applied under a host of clinical conditions, the presence of an emetic drug in a barbiturate formula must be considered deleterious to the patient. Such combinations administered to the postoperative or the obstetrical patient in labor, and others, in many of whom the emetic centers are already stimulated or in a critical state of imbalance, might well cause retching even when small therapeutic doses are employed. Finally, true accidental poisoning by the barbiturates as with all other potent drugs is rare. The seasoned habitué who conceivably might experience some gastric upset following ingestion of an emetic–barbituric acid combination would quickly seek illegitimate channels of supply providing barbiturates without the emetic component. As has been intimated, these sources would probably be abundant.

How Habituation Occurs. The layman may well find it difficult to comprehend how habituation to the barbiturates occurs. These individuals, as intelligent and thinking citizens, are interested in knowing whether the habitué is actually, as the tabloid journals have insisted, an innocent victim of an insidious and harmful drug. The physician called upon to correct habituation is concerned about the degree of psychic and histological damage which has taken place and how the patient may best be treated and rehabilitated. Conscientious physicians and laymen both seek a practical approach to the prevention of the condition.

It is, of course, impossible and highly imprudent to attempt to establish which single factor is chiefly responsible for the promiscuous use of this family of drugs. Unquestionably, the emotionally unstable patient seeking an escape mechanism represents the starting point in most instances. These people utilize the barbiturates or other medications which produce sedation or hypnosis in an attempt to escape realities and the everyday problems with which humanity is constantly confronted. Closely allied to the aforementioned group are the persons who take the barbituric acid derivatives in their endless search for "thrills" or "smart new things to do." Failing a barbiturate habituation, these same individuals probably would be alcoholics or addicted to marihuana, cocaine, or one of the opium derivatives. In many instances, the "alcoholic," "snow-bird" or "reefer" addict employs barbiturates as well.

Unquestionably, mild habituation may occur in a small minority who

have the drug prescribed regularly in a bona fide manner for some chronic disorder. The alert and conscientious physician will, however, follow with caution the course of any patient to whom he is prescribing sedative drugs of a habituating type, to prevent dependence on the agent. Substitute therapy with other families of sedative or hypnotic compounds, or cessation of medication (excepting in very severe cases) when symptoms of psychic disturbance or habituation appear, will be instrumental in preventing more serious complications later.

Regrettable as it may seem, there appear to be a few physicians who, because they are overworked, careless, or incompetent, substitute sedative or hypnotic drugs for a specific diagnosis and treatment in certain cases requiring intense study and continued observation. Apparently there also exists a minority of physicians who have no compunctions about prostituting their profession by supplying any drug or service for an adequate financial consideration. This statement may well elicit a challenge of proof. Yet it is not necessary to cite references to establish the conviction. We cannot discount the fact that licenses to practice medicine are constantly being revoked for infractions which run the gamut from abortion to the promiscuous and illegal dispensing of narcotics.

Unscrupulous individuals who "peddle" drugs unquestionably constitute the worst offends. Isbell *et al.*, in an excellent review on chronic barbiturate poisoning, cite several lay publications in which the inference is clearly established that "goof ball" salesmen, unscrupulous pharmacists, and drug peddlers are engaged in the lucrative albeit illegal trafficking in barbiturates. How the peddler procures the drug is a matter for speculation. The author is in the unique position of being able to review each year numerous cases concerning the abuse and promiscuous use of the barbiturates. Since certain confidences extended by law-enforcement bodies and investigators must be honered, detailed factual evidence in this respect, obviously, cannot be cited. It should herewith be strongly emphasized that most pharmacists maintain strictly ethical standards, for which they are to be commended, in dispensing barbituric acid derivatives. Yet not infrequently one reads of "chiselers who have no compunctions about selling these drugs without prescriptions, and usually at inflated prices. Recently a pharmacist in an Eastern metropolis was apprehended for openly displaying large receptacles containing two popular barbiturates with "sale" price tags clearly in evidence on each. It is a matter of common knowledge that shady characters, and even waiters in certain disreputable night clubs in many of our larger cities, openly sell barbiturates at prices ranging upward from one dollar each per capsule or tablet. Peddling of barbituric acid derivatives on high school and college campuses in some metropolitan areas apparently is not at all uncommon. Depending on the individual product characterized by its distinctive gelatin capsule color, such terms as "red devils," "yellow jackets," "blue boys," are employed.

Use of Barbiturates and Other Drugs. ALCOHOL. The concomitant use of alcohol and barbiturates purportedly produces an intense exhilaration of brief duration followed by profound intoxication and narcosis. Since the basic pharmacological responses of both drugs are sedative in nature, it can be assumed that the supposed exhilaration actually is nothing more than rapid release of inhibitions.

The synergistic effect resulting from the ingestion of the barbiturates and

alcohol is profound. Injudicious use of such combinations is extremely dangerous and frequently causes death, even though nontoxic quantities of each drug are ingested[5]. Pharmacological studies have shown that the lethal dose of any barbiturate is greatly reduced in the presence of alcohol levels sufficient to produce intoxication[3,11,16]. Ramsey and Haag[14] have shown that the LD_{50} (the amount of drug required to kill 50% of a test group of animals) of seconal sodium could be lowered from 140 mg. per kg. of body weight to 105 mg. per kg. of body weight in mice when the drug was administered concomitantly with alcohol. By the same token, analeptic drugs proved less efficacious when administered to animals having received a combination of pentobarbital sodium and alcohol than those having received the barbiturate only.

Use with Cerebral Stimulants. Perhaps an even more vicious and insidious practice consists of the ingestion of cerebral stimulants such as the amphetamine compounds upon arising and during the day, followed by heavy barbiturate medication at the time the individual retires. This practice is gaining favor and appears to be very common among "desk" workers under constant intense tension and pressure, entertainers, and chronic devotees to night life. The cycle, once established, is most difficult to correct. In this group, as well as those who utilize alcohol and the barbiturates concomitantly, are found most of the so-called unfortunate innocent victims of what the tabloid writers delight in branding "devil drugs." In a word, these people have deliberately acquired a habit which, to their way of thinking, will enable them to extract more out of their wakeful and sleeping hours than is physiologically normal. They not only burn the proverbial candle at both ends, but from the middle to the outside as well.

Recently, following the accidental death of an individual prominent in the theatrical world, after the ingestion of an undetermined but obviously very impressive amount of a barbituric acid derivative while the "victim" already was in a state of alcoholic intoxication, an investigation was instituted to determine whether the rumored promiscuity with these drugs was factual. The inquiry subsequently revealed that in the colony where the death had occurred, self-administration of up to 15 grains of popular short-acting barbiturates at what constitutes "the hour of sleep" was not at all uncommon among some individuals. Furthermore, it was found that in an attempt to overcome stupor and lethargy, upon being aroused by a dutiful servant for the next day's or night's activities, large amounts of cerebral stimulants were employed. Alcoholism usually completed the triumvirate, although the use of "reefers" and worse was frequently found to constitute an "added thriller." Obviously under these conditions, "accidental" poisoning and death occur rather frequently and another "innocent" victim assumes in the eyes of the sensationalist the role of a martyr. Isbell and his workers[8,9] have indicated that many of the patients presenting themselves for treatment at Lexington, Kentucky, ingest barbiturates on a day-to-day basis in quantities which equal or exceed the dosages referred to in one of the preceding statements. The practice does not, therefore, appear to be limited to a given geographical area.

Symptoms of Habituation. The patterns as outlined may, then, lead to the ultimate spectacle of the abject, decrepit, and ill individual who has become habituated to the barbiturates. For others, the pursuance of these follies may terminate fatally. The true

or advanced habitué's symptoms are readily recognizable. Psychoses are very evident and may be pronounced. Reflexes deviate from normal patterns. Personal hygiene is neglected, and the patient becomes careless about appearance and habits. Most severe "nervous" symptoms involve the motor tracts manifesting themselves as tremors, ataxia, dysarthria, faulty gait, and lack of coordination. Isbell *et al.*[9], in recent work discussing the above findings in a group of former narcotic addicts who had volunteered to participate in the experiment where large quantities of barbiturates were administered each day over a period of several months, describe in detail the course and nature of these symptoms in the test subjects. Fortunately, the symptoms are transitory. Rehabilitation is possible but difficult for reasons to be considered presently.

Treatment. The most important phase in this tragic drama concerns the manner in which these people should be treated and rehabilitated. As has been inferred, most of these individuals probably acquired the habit on the basis of psychic problems or instabilities of one kind or another. Most do not whole-heartedly wish to break their habit, even though treatment is sought. To do so would bring them back to realities which they would find difficult or impossible to cope with. This has led to the development of numerous therapeutic regimens designed to obliterate, if possible, the underlying causes having predisposed to the habituation.

Electro- and allied shock therapy represents one of these therapeutic measures. Treatment of this type is, admittedly, drastic and potentially hazardous from the standpoint of inflicting physical or further psychic damage. In expert hands, it apparently benefits some patients. If abused, it may well merely constitute another means of further bedevilling an individual who already is the victim of his own weaknesses and possibly the faulty scruples or carelessness of others. Rehabilitation regimens may be successful in certain cases through the employment of conservative methods solely. In these cases withdrawal of the drug, possibly judiciously applied substitute therapy, adequate diet, mental hygiene, and application of the principles of psychosomatic medicine should be conscientiously and carefully utilized. Whenever possible, the underlying causes predisposing to the habituation should be removed or corrected. Failing this, more drastic measures may be the only remaining alternatives. The problem at this point resolves itself into a single salient factor. Undo, if possible, the damage done, and in the most honest and therapeutically acceptable manner, institute therapy specifically selected for the particular patient in question. The method of treatment in a given case should never constitute a pattern for possible future application in other patients, since each problem will require individual study.

Treatment directed to overcoming habituation to the barbiturates will bog down helplessly if the patient does not in all seriousness wish to be cured. As might be anticipated, the number of patients who will unreservedly cooperate in rehabilitation regimens is limited. It is of prime importance that the physician impress upon his patient the irrevocable fact that the process of overcoming the habituation will be trying and not without discomfort. Abrupt withdrawal of any barbiturate from a patient who ingests impressive quantities daily is not without hazard[8,9]. The symptoms already described for the advanced syndrome may be markedly accentuated follow-

ing abrupt withdrawal of the drug. Some patients may experience convulsions. Substitution therapy with small carefully selected doses of other sedatives such as paraldehyde, the bromides and chloral hydrate, and others, may be helpful during the trying period, if regimens designed to utilize progressively decreasing quantities of the agent to which the habituation exists do not seem prudent for one reason or another. Isbell[8] most emphatically recommends that the treatment consist of gradual and progressive reduction in dosage of the barbiturate itself, adding that abrupt withdrawal is strictly contraindicated. Obviously, reliance on opiates as substitution therapy should be considered most unwise. Irrespective of the type and nature of the sedative or hypnotic utilized during the withdrawal process, the substitute agent should be entirely eliminated as soon as possible. In the therapeutic regimen, maintenance of nutrition and mental hygiene is imperative. Activity and exercise compatible with the patient's physical status and capacities should be encouraged.

Judicious Treatment of Insomnia. The conscientious physician who is so frequently called upon to prescribe for the simple insomnias present on the basis of excessive tension, worry, or lack of adequate physical exertion may well ponder long and seriously as to what to do for the patient who insists he cannot achieve sleep without some sedative or hypnotic each night. While the question of treatment in simple insomnia may appear vexing, most cases in this category can be corrected quite readily. The patient who requests a prescription for a barbiturate should be advised of the possible hazards attending the prolonged or oft-repeated use of any sedative or hypnotic drug. Such simple measures as a hot bath and glass of hot milk or chocolate just prior to retiring may be helpful in many cases. Adequate physical activity each day is, of course, mandatory. For the office or allied worker and the bridge-playing housewives whose maids have removed the need for them to expend any physical energy in the home, wholesome exercise and recreation, bringing with it natural fatigue, become imperative.

Where domestic or business problems contribute to insomnia, application of psychosomatic medicine may be indicated. One factor should always be borne in mind when a patient seeks relief from insomnia. Since everyone requires and usually gets a certain number of hours of sleep each 24-hour period on a year-in-year-out basis, attempts should be made to establish a normal rest pattern in each individual case. The patient who tosses about for lack of sleep and finally ingests a barbiturate at 2 or 3 o'clock in the morning invariably compensates for the rest lost prior to taking the medication. It is most likely that following the use of the hypnotic drug, he will sleep beyond his usual waking hour. Others may take time out during the day for brief cat-naps or retire earlier on the evening following the night of "lost sleep." It should be apparent that if the continued use of barbiturates is unchecked in these individuals, they may very quickly develop insidious patterns which can only lead to habituation.

Physical and Psychic Changes. A question paramount in the minds of many physicians is whether or not the prolonged use of large quantities of a barbiturate may bring about damage to brain and other tissues. It is logical to assume that the long-acting barbiturates such as phenobarbital and barbital, both of which remain in the tissues for 48 or more hours after a single dose and are dependent on the

kidney for excretion, might well impair the physiological function of that organ if impressive quantities are utilized for long periods of time. It has long been accepted that any barbiturate excreted by the kidneys is contraindicated if extensive renal damage exists.

Some years ago Seevers and Tatum[17] carried out a study in animals in which long-acting barbituric acid derivatives such as barbital were administered in 100 mg. per kg. doses daily over a 3½ year period. When the dogs were eventually sacrificed, definite pathological changes in brain and nervous tissues were observed More recently, Swanson, Weaver, and Chen[18] administered 1/3 of the minimal lethal dose (animal) of a moderately long-acting barbiturate to a number of dogs 3 days per week for a period of 20 weeks. At the end of the study, the dogs were sacrificed. At autopsy there was no evidence, gross or microscopic, of tissue damage in the liver, kidneys, brain, spinal cord, or elsewhere, which could be directly attributed to the action of the drug. Jervis and Joyce[10] have described a case which terminated fatally following the prolonged use of relatively large quantities of an opiate and barbiturates. When the case came to autopsy, it was revealed that definite pathological change existed in the brain and spinal cord. Creutzfeldt[1] observed a similar case. Petri[13], Hassin[7] and De Groat[2] have reported cases in which unmistakable pathological changes were in evidence in patients having succumbed to overdosage with phenobarbital or barbital. While it is not the purpose of this paper to discuss the nature of the pathological lesions or their predisposing factors, cerebral anoxia appears to be the prime factor when the changes alluded to occur.

The findings just presented suggest that the shorter-acting barbiturates possibly are more completely metabolized in a shorter period of time and thus are less apt to prolong cerebral anoxia for protracted and dangerous periods. Obviously, this is merely an observation and should not be construed to mean that the shorter-acting agents are innocuous if employed to excess. The work carried out by Isbell *et al.*[9] at Lexington, Kentucky, revealed that definite personality changes had occurred in all test subjects in their series. It, therefore, behooves us to bear in mind that "psychic damage," which under certain circumstances may be more difficult to cope with than actual "tissue damage," may well develop in all or most cases in which large amounts of any drug producing escape from realities are repeatedly ingested over long periods of time.

Summary of Methods of Prevention. A panacea can never be hoped for in the correction and prevention of these conditions. National legislation to control distribution is probably inevitable. In the meantime, careful and intelligent cerebration when this family of drugs is prescribed is of paramount importance. Cooperation between the physician and pharmacist is not only desirable but mandatory. These steps, together with the honest desire to evaluate and treat each case individually, plus conscientious efforts on the part of everyone affiliated with the distribution of these drugs to stamp out the roots of evil when they are encountered, must be achieved. Such action will probably do more to abolish a most unfortunate situation than will well-meant but often poorly conceived legislation or the ill-advised portrayals by the tabloid journals.

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THE EFFECTS OF INTRAVENOUS PROTOVERATRINE ON HEMODYNAMICS AND EXERCISE TOLERANCE IN PATIENTS WITH HYPERTENSION

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The use of *Veratrum viride* for the moderation of essential hypertension has recently been reviewed by Wilkins[7]. According to the experience of this author various preparations were found to be palliative rather than curative, and the hypotensive effects resulting from continuous treatment were less impressive than the initial responses. The dosage employed was rather critical for each patient, and salivation, nausea, and vomiting ensued from overdosage. About 80% of the patients exhibited some degree of hypotensive response. Regardless of which preparation was used, only rarely was the arterial pressure restored to normal after treatment with veratrum. Some patients exhibited a decrease in cardiac enlargement, improvement in competence, and electrocardiographic abnormalities. Retinopathy was decreased and renal function has remained adequate except in instances of progressive chronic nitrogen retention. No evidence of tolerance or idiosyncrasy to the drug was found. The most satisfactory mode of administration was by mouth, after meals, and at bedtime. Occasionally collapse occurred in spite of extreme care with the dosage. Ephedrine (30 to 45 mg.) was an effective antidote for collapse, just as atropine (0.5 to 1.0 mg.) counteracted marked bradycardia. The hypotensive effects of active preparations of *Veratrum viride* were believed to be due to centrally mediated vasodilation.

Krayer and associates[4] used crystalline alkaloids of veratrum and found the action to be due to reflexes involv-

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ing peripheral endings of the vagus nerve. They found that bradycardia was a viscero-motor effect which could be separated from the hypotensive effect produced by atropinization in man, or vagectomy in the dog. The cardiac output may have been increased in those patients in whom the output was low due to congestive failure. Initially the renal and hepatic blood flow often diminished with the first fall in arterial pressure, subsequently returning to control values when the blood pressure stabilized. *Veratrum viride* did not alter postural adaptations or vasomotor reflexes and it was found not to be sympatholytic.

Similar hypotensive effects have been reported from the parenteral administration of protoveratrine[5]. This substance is a crystalline derivative of *Veratrum album*, and has the advantage of being a single compound. It is the purpose of this report to describe the effects of protoveratrine on the hemodynamics and exercise tolerance in patients with hypertension.

TABLE 1.—PHYSICAL AND CLINICAL CHARACTERISTICS OF PATIENTS WITH ESSENTIAL HYPERTENSION

Patient	*Age*	*Sex*	*% Deviation from Ideal Weight*	*Resting Blood Pressure (mm. Hg)*	*Duration of Hypertension (years)*	*Predominant Symptoms*	*Retinopathy*	*Complications*
GROUP 1								
W. W. S.	59	M	18%	139/93	1	0	0	0
L. J. F.	31	M	19%	144/105	5	0	0	0
P. M.	67	M	Normal	264/197	20	Exertional dyspnea orthopnea	Min.	Congestive failure ? Myocardial infarction
E. R.	39	F	Normal	150/110	5	Dizziness, fatigue headaches	Min.	0
R. W.*	55	F	22%	207/106	14	Headache, vertigo, dyspnea, angina, edema, nocturnal dyspnea	Mod.	Cerebral vascular accident congestive failure; auricular fibrillation
B. S.	58	F	4%	182/127	10	Palpitation of heart	**	Dissecting aneurysm (old)
J. W.	35	M	6%	182/110	2	0	Mod.	Congestive failure
J. G.	53	M	Normal	168/92	4	Headaches, dizziness	Min.	0
C. B.	38	F	2%	140/86	¼	Dizziness, throbbing	Min.	0
A. F.	73	F	19%	188/90	20	Headache, angina, dyspnea, edema	Min.	Coronary insufficiency
GROUP 2								
E. R.	39	F	Normal	150/110	5	Dizziness, headache, fatigue	Min.	0
E. N.	57	F	3%	211/120	6	Headache, throbbing epistaxis	Mod.	Vitreous hemorrhage, right eye
R. A.	56	M	10%	174/122	7	Headache, palpitations	**	0
A. F.	73	F	19%	188/90	20	Headache, angina, edema, dyspnea	Min.	Coronary insufficiency Congestive failure
A. E. F.	67	M	5%	188/98	4	Dizziness, dyspnea, weakness	**	Mild congestive failure
E. M.	51	M	34%	157/108	7	Headache, dyspnea, dizziness	Mod.	0
C. B.†	47	M	9%	219/137	10	Confusion, dyspnea, edema, nocturnal dyspnea	0	Encephalopathy
C. P.†	47	M	21%	202/119	14	Confusion, edema, dyspnea, weakness	0	Congestive failure Renal disease
I. W.	65	F	18%	218/127	6	Headache, edema, angina	Mod.	0

* Bilateral Smithwick operation 4 years ago.
† Chronic renal disease.
** Not examined.

Material and Methods. The physical and clinical characteristics of 19 hypertensive patients are shown in Table 1.

Exercise tolerance was tested by means of walking for 10 minutes on a motor-driven treadmill on a 10% grade at the rate of 1.73 mph. Continuous ventilatory, respiratory, circulatory, and electro-cardiographic observations were made during the adaptation to and recovery from exercise as previously described.[1] The working capacity was estimated from the physical fitness index[2] as follows:

$$\text{Physical Fitness Index} = \frac{\text{Respiratory efficiency} \times \text{endurance time (min.)}}{\text{Total heart rate for first 3 minutes of recovery}}$$

Each test included observations at 1 minute intervals during 5 minutes of rest, walking for 10 minutes, and 3 minutes of recovery. For those patients unable to walk for 10 minutes, exercise was continued only as long as it could be endured.

Two control observations of exercise tolerance were made, usually on consecutive days. Protoveratrine* (diluted in 10 ml. of normal saline solution) was given intravenously about an hour after the 2nd exercise tolerance test had been completed. In the first 10 patients, (Group 1), resting observations were made while the patient was recumbent and immediately before, and at 0, 3, 6, 9, 12, 15, and 20 minutes following the intravenous administration an average dose of 0.12 mg. of protoveratrine. These observations included determinations of arterial blood pressure, pulse, and respiratory rates, and in several instances venous pressure. Following this another exercise tolerance test was performed.

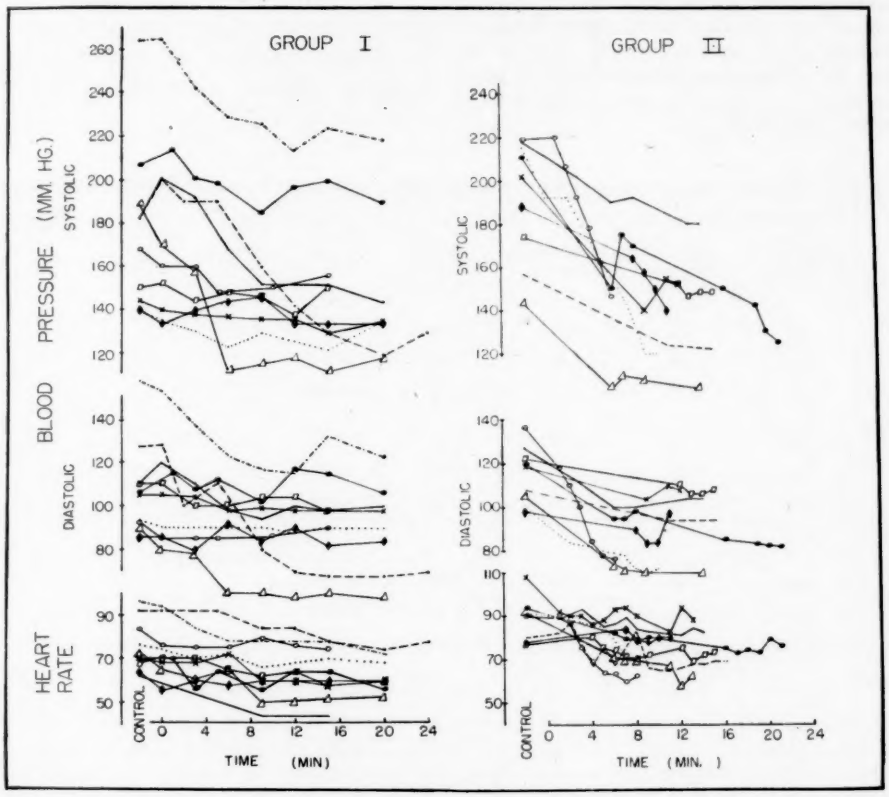

FIG. 1—The immediate effects of intravenous protoveratrine on the blood pressure and heart rate for all the patients in both groups.

* Courtesy of Dr. K. G. Kohlstaedt, Eli Lilly and Co., Indianapolis, Indiana.

Because of the relative paucity of significant changes on this regimen, 9 more patients were given this compound intravenously after the control exercise test (Group 2). As soon as the blood pressure declined and the heart rate slowed, the test was repeated. If a hypotensive effect had not occurred, another dose was given. The average dose of protoveratrine was 0.19 mg. The maximum single dose was 0.2 mg., and the maximum total dose was 0.3 mg.

The gradient for oxygen between end-tidal expired air (alveolar) and arterial blood was determined for several patients before and after the intravenous administration of protoveratrine, according to the technique described eleswhere[6].

The average values of the components measured during the exercise tests are presented in Table 2. In this group most of the changes following protoveratrine were as variable as the changes between the two control tests. The average heart rate during exercise and also the total heart rate for the first 3 minutes of recovery were lower.

The effect of protoveratrine on the gradients for oxygen and CO_2 between end-tidal expired air (alveolar) and arterial blood showed considerable variation (Table 3).

TABLE 2.—AVERAGE VALUES OF VARIOUS COMPONENTS MEASURED IN THE EXERCISE TOLERANCE TEST

	Oxygen Consumption cc./M²/min.	*Heart Rate/min.*	*Respiratory Efficiency*	*Ventilation L/M²/min.*	*Blood Pressure S/D*	*Oxygen Transport cc./beat*	*Duration of Exercise (min.)*	*Recovery Heart Rate (first 3 min.)*	*Physical Fitness Index*
GROUP 1									
REST									
A	142	87	3.71	3.98	180/114	1.66			
B	147	88	3.89	4.20	170/107	1.69			
C	141	77	3.83	4.02	156/105	1.79			
EXERCISE									
A	476	122	4.22	11.46	205/122	4.01	6.9	312	10.7
B	480	123	4.57	10.65	191/107	3.78	7.5	305	11.8
C	475	112	4.68	10.43	181/112	4.40	8.0	275	13.9
GROUP 2									
REST									
A	150	86	3.93	3.85	196/116	1.77			
B	151	90	3.61	4.39	185/109	1.66			
C	154	75	3.36	4.69	134/85	2.06			
EXERCISE									
A	473	121	4.62	9.95	227/121	4.15	7.2	316	11.7
B	499	127	4.58	11.06	223/118	3.83	7.3	329	11.2
C	481	108	4.74	10.28	168/96	4.45	6.9	260	13.4

A = First control.
B = Second control.
C = Post-protoveratrine.

Results. GROUP 1 (PROTOVERATRINE INTRAVENOUSLY IN RECUMBENT POSITION). Only 4 of the 10 patients had more than a 10% decline in either systolic or diastolic pressure over that of the control (Fig. 1). The random changes in the others were not significant. There was a decline in the heart rate of more than 10% from the control value in 9 of the 10 patients.

GROUP 2 (PROTOVERATRINE INTRAVENOUSLY WITH PATIENT SITTING IN CHAIR). Fig. 1 shows the effects on the blood pressure and heart rate, within 15 minutes from the administartion of protoveratrine. The hypotensive effect and bradycardia were more apparent than in Group 1. All of the 9 patients had more than a 10% reduction in either systolic or diastolic pressure. Seven

showed more than a 10% decline in heart rate. The hypotensive effect was sustained during exercise (Table 2). In addition there were more nearly normal exercise values for respiratory efficiency, minute ventilation, average heart rate, recovery heart rate, and physical fitness index (Fig. 2). One patient developed precordial pain and could walk for only half as long as before.

The following 2 cases illustrate the potential hazard of indiscriminate use of a hypotensive drug such as protoveratrine intravenously.

TABLE 3.—EFFECTS OF PROTOVERATRINE ON CARBON DIOXIDE AND OXYGEN TENSIONS OF END-TIDAL EXPIRED AIR AND ARTERIAL BLOOD DURING REST*

	End-Tidal Air mm. Hg		*Arterial Blood mm. Hg*		*Gradients mm. Hg*	
Patient	pCO_2	pO_2	pCO_2	pO_2	pCO_2	pO_2
P. M.	25–24	116–114	43–38	54–49	18–14	62–65
R. W.	35–35	104–103	50–43	82–83	15–8	22–20
J G.	29–26	117–120	37–53	80–83	8–27	37–37
L. W.	—	109–110	53–38	82–93	—	27–17
J. M.	—	106–108	41–39	92–91	—	14–27
H. P.	29–31	103–107	31–39	73–79	2–8	30–28
AVERAGE	30–29	109–110	43–42	77–79	11–14	32–32

* The values in the first and second columns of each section represent these before and after protoveratrine injection, respectively.

CASE 1. A. E. F. (Table 1) tolerated the 2 control exercise tests for 10 minutes without chest pain. The patient was given 0.1 mg. of protoveratrine intravenously while sitting in a chair on the treadmill. After 12 minutes the blood pressure had dropped to 138/94. The exercise was started. After 5 minutes he had to stop walking because of dizziness and a burning sensation beneath the sternum. This distress persisted for 2 or 3 minutes. Fig. 2 shows representative samples of the precordial electrocardiograms during the second control and the post-protoveratrine exercise tests. In both sets of tracings there was depression of the ST segments during exercise, such as is commonly seen in patients with coronary insufficiency. After the 4th minute of exercise there was a marked difference in the post-protoveratrine tracings. In the 5th minute, when he was complaining of substernal distress, the QRS voltage was diminished and the T waves became high and peaked. These changes reverted by the 4th minute of the recovery period. The blood pressure in the 4th and 5th minutes of recovery was 206/90 and 210/98, respectively, and by this time his distress had disappeared. High peaked T waves during exercise have previously been seen in patients with coronary insufficiency[8] and, the writers believe, are an early manifestation of acute subendocardial ischemia.

CASE 2. C. B. was a 47-year-old man who had had sustained hypertension for the last 10 years. He had a history of nephritis in the past complicated lately by a suggestive history of myocardial infarction on 2 occasions, hypertensive retinopathy, and encephalopathy. He was admitted to the hospital in May, 1950, for symptoms of mild congestive failure which cleared with bed rest and diuretics. Retrograde urographic studies showed a hydro-nephrosis of the right kidney. Both a right nephrectomy or a sympothectomy were considered but not performed because it was felt the patient was a poor surgical risk.

Three months after this admission he was seen in the Chest Laboratory. His resting heart rate and blood pressure during the 2nd exercise tolerance test were 92 and 226/140, respectively. He was able to walk only 1½ minutes because of dyspnea. Meanwhile, the pulse rose to 113 and the blood pressure to 250/140. The physical fitness in-

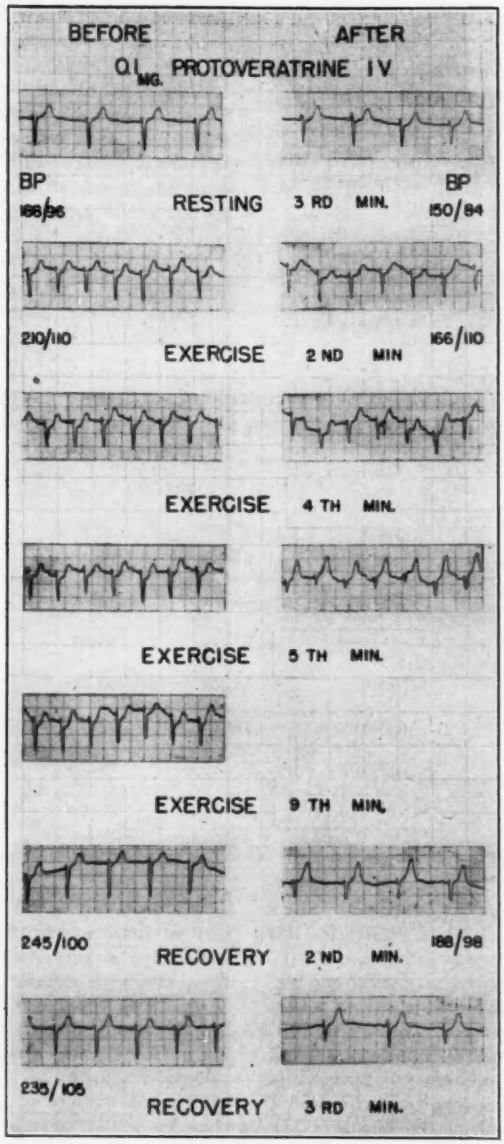

FIG. 2.—Case 1. Left, control exercise electrocardiogram. Note RS-T depression during exercise and no significant change in T wave. Right, post-protoveratrine exercise electrocardiogram. The tracings were taken up to the 5th minute of exercise. In addition to the RS-T depression, there are marked increase in the amplitude of T wave and decrease in the amplitude of QRS complex during the 5th minute of exercise and early recovery.

dex was markedly reduced to 0.9 (normal range 13 to 24). Following the intravenous injection of 0.2 mg. of protoveratrine the resting heart rate and blood pressure fell to 59 and 146/76, respectively. His exercise tolerance time increased to 2¼ minutes, the average exercise pulse was only 76, and the blood pressure was 152/87 with a physical fitness index of 3.1. However, the marked hypotensive effect resulted in myocardial ischemia probably due to a decrease in the coronary blood flow, as shown by the electrocardiographic changes in Fig. 3. Three minutes after the drug had been given the T wave in the

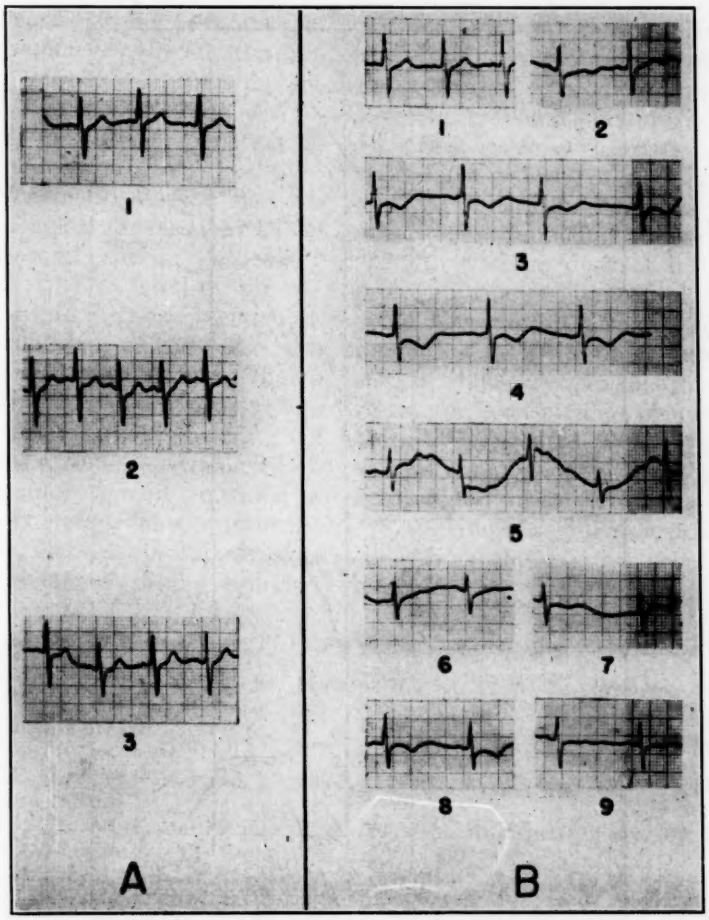

FIG. 3.—Case 2. A. Control electrocardiogram: 1, before exercise; 2, 2nd minute of exercise; 3, 3rd minute of recovery. Note the depression of RS-T segment during exercise. There is no significant change in the T wave.

B. Post-protroveratrine electrocardiogram: 1, before protoveratrine, resting; 2, 3 minutes after protroveratrine (p. p.), resting, T wave being inverted; 3, 8 minutes p. p., resting, showing nodal rhythm; 4, 11 minutes p. p., resting; 5, 15 minutes p. p. and 2nd minute of exercise; 6, 16 minutes p. p. and 1st minute of recovery; 7, 18 minutes p. p. and 3rd minute of recovery; 8, 26 minutes p. p. and 11th minute of recovery; 9, 65 minutes p. p.

After intravenous injection of protoveratrine there was marked inversion of the T wave which became upright during exercise and early recovery. Shifting of the base line of the tracings in 5, 6, and 7 was mainly due to respiratory movement. During the 11th minute of recovery, the T wave was again inverted. More than 1 hour after the protoveratrine injection, the T wave became slightly upright.

XUM

precordial lead had become inverted. This is similar to, but more marked than, the previously reported electrocardiographic changes following intravenous injection of protoveratrine[4]. The inversion of an upright T wave in the precordial lead is indicative of subepicardial ischemia.[3] However, during exercise the inversion became less marked and in the first minute of recovery the T wave was upright. By the 11th minute of recovery it was deeply inverted again. This parodoxical change of T wave during exercise was similar to that seen in Case 1 and is indicative of predominantly subendocardial ischemia.[3] This T wave change did not occur in the control exercise electrocardiograms.

Fig. 4 illustrates changes during exercise before and after intravenous protoveratrine observed in a typical case from Group 2.

Discussion. Although considerable individual variations in response were observed, the findings of Meilman and Krayer regarding the ability of protoveratrine to lower the blood pressure and slow the pulse have been confirmed to some degree. The responses generally speaking were not marked, and they did not persist for a sufficient

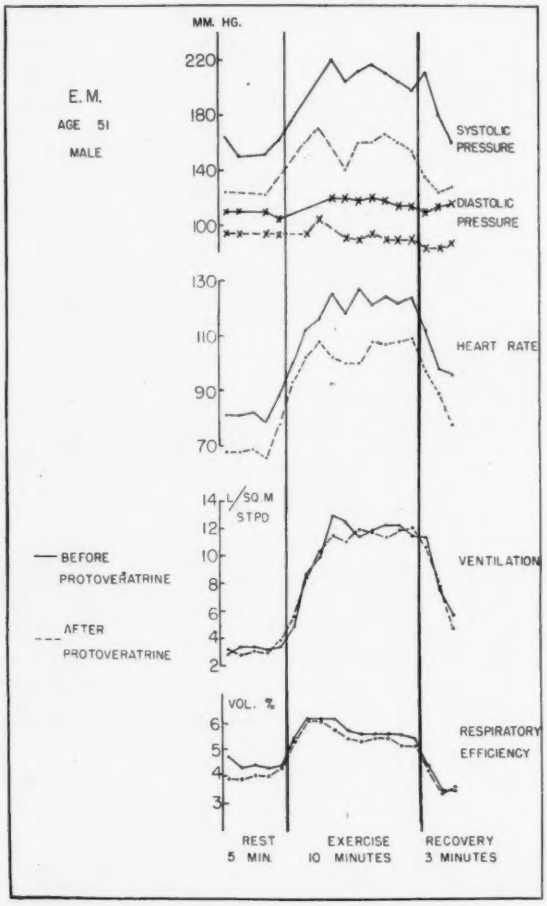

FIG. 4.—Minute-by-minute performance of representative exercise tolerance testing of patient E. M. The solid lines represent the results of a control test, while the dotted lines show the performance after intravenous protoveratrine.

length of time to prove efficacious therapeutically. The toxic symptoms of nausea and vomiting were not obtained, although questionable nausea was noted by 2 patients. More serious untoward effects were observed in 2 patients who manifested characteristic electrocardiographic evidence of coronary insufficiency. In addition nodal rhythm ensued. Presumably the lowering of the blood pressure was responsible for a critical reduction in coronary blood flow.

It is interesting to observe that the usual physiological increase in blood pressure during exercise (especially systolic) was not prevented by the use of protoveratrine. Similarly, the physiological acceleration of the pulse also occurred. But in each instance that a significant pharmacologic response was obtained, usually by administering 0.2 mg. of protoveratrine intravenously, an appreciable improvement in exercise tolerance was noted. This was measured by the increase in the average respiratory efficiency during exercise, as well as the more rapid slowing of the pulse during recovery. Presumably not only was the peripheral resistance diminished, but the effective resistance of the tissues was increased, with less work for the heart.

Summary. 1. An average dose of 0.12 mg. of protoveratrine injected intravenously in a group of hypertensive patients failed to produce at least a 10% lowering of blood pressure in 6 out of 10 cases. A relative bradycardia occurred in a majority of the group. There was no effect on exercise tolerance other than a reduction in heart rate.

2. An average dose of 0.19 mg. of protoveratrine administered intravenously in another similar group produced more than a 10% drop in blood pressure in all 9 cases. In this group there were more conspicuous changes in exercise tolerance as measured by the various components of the physical fitness index.

3. Deleterious electrocardiographic changes during exercise occurred in 2 patients.

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XUM

TREATMENT OF THYROTOXICOSIS WITH METHIMAZOLE* (1-METHYL-2-MERCAPTOIMIDAZOLE)

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and

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Recently, Stanley and Astwood[4,5] reported 1-methyl-2-mercaptoimidazole to be a potent antithyroid drug as measured by its ability to inhibit the rate of uptake of radioactive iodine by the human thyroid gland. Clinical trials soon followed.

McGavack and his associates[2] concluded that methimazole (1-methyl-2-mercaptoimidazole) was the antithyroid drug of choice in patients with hyperthyroidism; they found it to be highly potent, rapidly active, and nontoxic. Reveno and Rosenbaum[3] reported the treatment of 18 patients using dosages of 2 to 5 mg. of methimazole every 8 to 12 hours. They reported satisfactory response and no toxicity. Beierwaltes[1] reported on 9 patients receiving methimazole and 11 patients receiving a related compound (1-ethyl-2-mercaptoimidazole). He concluded that these mercaptoimidazole drugs appear to be equal in effectiveness and are over 7 times as effective as propylthiouracil by weight. In his series, return to the euthyroid state was rapid; there were no toxic effects of the medication, and there was no progressive enlargement of the thyroid gland. However, an increase in exophthalmos occurred in 3 of the 4 patients adequately studied.

When methimazole was made available to the authors for evaluation as an antithyroid drug, their previously reported study[6] of hyperthyroidism was continued by employing this new medication.

This preliminary report is presented because the results in the first 23 patients demonstrate that methimazole is a very effective antithyroid drug, is free from toxicity, induces the euthyroid state rapidly, and is thus superior to propylthiouracil.

Method. As in the previous study with propylthiouracil, patients with diffuse goiter and hyperthyroidism are assigned alternately for surgical and medical treatment. If there are no contraindications, the patients with nodular goiters undergo subtotal thyroidectomy when they become euthyroid. Treatment is started in all patients with methimazole, 10 mg. every 8 hours. This dose is increased to a maximum of 15 mg. every 6 hours if the response is slow. Those in the surgical group are operated upon when the euthyroid state is reached. Those in the medical group are carried on maintenance doses of the drug with the hope that a sustained remission will occur after 8 to 12 months of euthyroidism on treatment.

Results. Twenty-three patients have been treated with methimazole since June, 1950. Up to the present time, 15 have attained euthyroidism, 2 have

* This preparation under the trade name "Tapazole" (methimazole, Lilly) was supplied to the authors through the courtesy of Dr. Don Carlos Hines of Eli Lilly and Co.

failed to return to the clinic, and the remainder are continuing treatment.

There were 17 patients with diffuse goiter and hyperthyroidism who showed an average initial basal metabolic rate of + 41%; 12 of them have become euthyroid. The average duration of treatment until their basal metabolic rate was normal was 2 months, with an average total dose of 2 gm. of methimazole. Exophthalmometer readings showed no significant change in 9 of 15 cases which were studied adequately, while 6 cases showed a definite decrease. Slight enlargement of the thyroid (1 to 2 cm. increase in neck circumference) occurred in 5 cases on methimazole therapy, while 9 showed no change and 1 showed a decrease in neck circumference of 2 cm.

There were 6 patients with toxic nodular goiter. Their initial basal metabolic rates averaged + 43%. Three of them have become euthyroid and have been operated upon. Their average duration of treatment was 87 days, and their average total dosage of methimazole was 3.025 gm.

Cardiac complications, present in 7 of the diffuse and 3 of the nodular cases, have all responded satisfactorily during the period of methimazole treatment.

Toxic reactions did not appear in any patient during this 6-month period of observation. Indeed, no undesirable effects of any kind have been noticed except for the slight increase in size of the thyroid, which has already been mentioned.

Several illustrative case reports follow:

Case Reports. CASE 1. H. B., a 32-year-old colored female, was admitted to the hospital May 22, 1950, with history and physical findings typical of diffuse goiter with hyperthyroidism. Basal metabolic rate determinations were +44% and +42%. Exophthalmos was present, both eyes measuring 21.5 mm. on the Hertel exophthalmometer. Biopsy of the thyroid gland revealed diffuse hyperplasia.

The patient was assigned to the medical group and given methimazole, 10 mg. every 8 hours. After 4 months all symptoms of hyperthyroidism had disappaared and the basal metabolic rate was —4%. The methimazole has been continued until the present and euthyroid status has been maintained. Biopsy of the thyroid was repeated 5 months after treatment was begun; the gland appeared somewhat less hyperplastic than it had prior to treatment. Exophthalmos decreased while this patient was being treated, so that by the time the basal metabolic rate was normal, the right eye measured 17 mm. and the left 18 mm., decreases of 4½ and 3½ mm., respectively. The patient remains free of symptoms.

CASE 2. J. C., a 22-year-old colored female, was admitted to the hospital July 13, 1950, with a 3-month history of hyperthyroidism. Examination revealed a diffusely enlarged thyroid gland and evidence of moderately severe hyperthyroidism. There was no exophthalmos. The basal metabolic rate determinations were +58% and +54%. She was given methimazole, 10 mg. every 8 hours, and responded well, the basal metabolic rate dropping to +3% after 90 days of treatment. She continues to take methimazole and is asymptomatic.

COMMENT. Except for the rather slow response to treatment, the uncomplicated courses observed in these 2 patients are quite typical of the entire series.

CASE 3. H. J., a 32-year-old colored male, was admitted to the hospital June 3, 1950, because of severe hyperthyroidism with a basal metabolic rate which checked on 2 determinations at +68%. There was slight diffuse enlargement of the thyroid gland. Exophthalmos was not present. While the patient was under observation, impending thyroid crisis was suspected and intravenous sodium iodide was administered. Improvement followed, and Lugol's solution, 10 drops 3 times daily, was given orally for 2 weeks. Methimazole, 10 mg. every 8 hours, also was begun 1 week after institution of the iodine treatment, and after 7 days of combined therapy with methimazole and iodides the basal metabolic rate was +26%. Methimazole was continued and the patient followed in the clinic. Two months later the basal metabolic rate was —6% and the patient was

asymptomatic. Lugol's solution again was given for 2 weeks and thyroidectomy was performed. The post-operative course was uneventful and the patient remains well, with basal metabolic rates ranging from −9% to +6%.

COMMENT. The relatively short period of methimazole therapy required to produce euthyroidism after initial iodine treatment of a severely thyrotoxic patient suggests that this method might be of value routinely. Further, this is consistent with unpublished results of the authors in a group of propylthiouracil-treated patients who received Lugol's solution during the first 2 weeks of therapy. The response was more rapid than with propylthiouracil alone.

CASE 4. P. M., a 52-year-old colored male, was admitted to the hospital on August 6, 1949, with a diffusely enlarged thyroid gland and clinical manifestations of moderate hyperthyroidism. The basal metabolic rate was +45%. Propylthiouracil, 100 mg. every 8 hours, was prescribed, and 2 months later the basal metabolic rate was normal. This treatment was continued for 8 months of euthyroidism and then discontinued. Relapse of the hyperthyroidism occurred within 2 months and the basal metabolic rate rose again to +45%. Methimazole then was given in doses of 10 mg. every 8 hours. Three months have elapsed since this treatment was begun. The thyrotoxic symptoms have subsided and the basal metabolic rate is +19%.

COMMENT. Response to methimazole in this case has been slower on retreatment of the relapsed hyperthyroidism than it had been initially with propylthiouracil. This has been noted in other instances during retreatment with propylthiouracil; frequently resistance to large doses of propylthiouracil has been encountered. Starting retreatment with larger doses of methimazole is doubtless indicated, but for uniformity in this study all patients have begun therapy on 10 mg. every 8 hours.

Discussion. The results of treatment of hyperthyroidism with methimazole may be compared to those obtained with propylthiouracil[6]. Thus far, except for a slight goitrogenic effect, the undesirable effects of propylthiouracil therapy have not been encountered. Of particular interest is the rapidity of response to methimazole, euthyroid status being reached in approximately 40% of the time and with about 6% of the dose of propylthiouracil (Table 1). Because of this, the degree of cooperation was much greater and more patients continued their therapy. Furthermore, no patients have been resistant to methimazole. Two of these patients had previously received 900 mg. propylthiouracil daily without satisfactory response. No explanation

TABLE 1.—COMPARATIVE DATA IN THYROTOXIC PATIENTS TREATED WITH METHIMAZOLE OR WITH PROPYLTHIOURACIL

	Methimazole	*Propylthiouraci*
Number of patients	15*	28
Average initial BMR	+41%	+55%
Duration of treatment to normal BMR	62.6 days	153.5 days
Total dosage	2.013 gm.	35.37 gm.

* 12 diffuse and 3 nodular goiters.

TABLE 2.—EFFECT ON EXOPHTHALMOS IN THYROTOXIC PATIENTS TREATED WITH METHIMAZOLE OR WITH PROPYLTHIOURACIL

	Methimazole	*Propylthiouracil*
Number of patients	15	22
Decrease in exophthalmos	6	3
No change in exophthalmos	9	11
Increase in exophthalmos	0	8

is offered for the absence of increasing exophthalmos in the methimazole treated cases as compared to the propylthiouracil group (Table 2). These findings are at variance with those reported by Beierwaltes[1], but neither series is large enough to be significant statistically.

Conclusion. Twenty-three patients with hyperthyroidism have been treated with 1 - methyl - 2 - mercaptoimidazole (methimazole). Response was rapid and uncomplicated as compared to the response in patients treated with propylthiouracil. The series is small and the period of observation short, but the results are so encouraging that further clinical trial of this antithyroid agent seems justified.

Dr. Gordon B. Myers, Professor of Medicine, and Dr. Charles G. Johnston, Professor of Surgery at the Wayne University College of Medicine gave helpful assistance throughout this study.

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LOCALIZED MYXEDEMA IN RELATION TO THYROTOXICOSIS AND EXOPHTHALMOS*

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The peculiar condition known as localized myxedema, characterized by the appearance of indurated plaques on the legs of persons who have, or have had, thyrotoxicosis[14], has excited considerable attention in recent years. Although productive only of cosmetic symptoms, the lesion is important as it is thought to be a manifestation of disease of the pituitary–thyroid axis which, like exophthalmos, cannot be ascribed to overproduction of the thyroid hormone. Hence knowledge of its pathogenesis might help elucidate the pathogenesis of the exophthalmos with which it is invariably associated[16]. In a personal communication, Means[8] has suggested that localized myxedema occurs in patients who have previously been hyperthyroid and who revert to a euthyroid or hypothyroid state. The rapidity of this deceleration may be an important factor in the evolution of the localized myxedema.

Characteristically, the lesions occur most commonly over the anterolateral aspect of the lower 3rd of both legs, but may involve the dorsal surface of the feet or the upper legs. The size varies considerably from barely visible plaques to diffuse irregular swellings involving the entire circumference of the leg[15]. The earliest lesions may best be detected by palpation, revealing a well-demarcated area of thickened skin. Later, the lesions typically become irregularly elevated with dilated hair follicles simulating pigskin. An advanced case may actually resemble lymphedema. The color varies from yellow waxy pallor to erythema. The edema is characteristically non-pitting.

The microscopic picture varies with the severity of the lesion[1]. The earliest changes are represented by edema of the upper cutis with slight fragmentation of the collagen bundles giving the appearance of "teased tissue". Unidentified stellate-shaped cells are scattered throughout the cutis between the fragmented collagen. Round cell infiltration is commonly seen about the smaller arterioles. Special stains for mucin reveal that this substance has infiltrated between the collagen bundles, around the sweat glands, and occasionally within the walls of the smaller blood vessels. As the lesion progresses, more splintering of the collagen fibers occurs, and, as the

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edema increases, there may be flattening and atrophy of the epidermis. Hyperkeratosis is common.

Recently it has been recognized that localized myxedema occurs frequently in association with progressive exophthalmos[1,13]. Therefore its presence should arouse suspicion that the exophthalmos is, or may become, progressive; in that event treatment of the thyrotoxicosis should be subordinated to protection of the eyes.

Cases of localized myxedema are rare or are rarely recognized. Up to 1949 less than 100 cases had been reported in the literature[4,9]. Many of these have been studied principally from the dermatological viewpoint and are incomplete in their reference to the endocrine component[15]. Only 10 cases of localized myxedema associated with progressive exophthalmos had been reported up to 1949[1,16]. The authors had the opportunity in the last year of studying 4 cases of localized myxedema, 3 of which were associated with progressive exophthalmos. Each case was different in some important respects (Table 1). The cutaneous lesion of each patient was studied by biopsy. In 2 patients the localized myxedema was early, and the belief was confirmed that the histological findings regarded as characteristic of localized myxedema signify a more advanced stage of the lesion[12].

TABLE 1.—SUMMARY OF FINDINGS IN 4 CASES EXHIBITING LOCALIZED MYXEDEMA

Case	*Age, Sex Race*	*Previous Thyroidectomy*	*Past Status of Thyroid*	*Present Status of Thyroid*	*Exophthalmos*	*Localized Myxedema*	*Serum Iodine in Gamma*	*BMR in % and Cholesterol in mg./100 cc. at Same Dates*		
								Time	*BMR*	*Cholesterol*
1	57 male white	None	No history of thyrotoxicosis	Euthyroid	Onset explosive. Extremely malignant. Loss of 1 eye despite surgical decompression	Onset unknown. Moderately advanced. Persists to present	6.5	Admission 1 month later	Unsatisfactory (+)23 (+)20	322 382
2	25 male white	1	Thyrotoxicosis preoperatively. Recurrence 8 months postoperatively	Mild thyrotoxicosis on propylthiouracil	Benign. Not progressive, but obvious	Onset unknown. Lesions very early. Recent regression	10.2	Pre-op. Postop. Readmission At present	(+)77 (−)19 (+)38 (+)19	160 400 239
3	37 male white	1	Thyrotoxicosis preoperatively. Myxedema postoperatively	Euthyroid on 2 grains thyroid extract daily; mildly hyperthyroid on 4.5 grains daily	Onset unilateral, progressive. Later bilateral, malignant. Controlled with thyroid extract	Onset 11 months postoperatively with exacerbation of exophthalmos. Moderately advanced. Recent regression	6.2	Pre-op. Admission Recent	(+)40 (−)6 (+)11	Not done 218 242
4	27 male white	3	4 episodes of thyrotoxicosis, 3 postoperatively	Euthyroid without therapy	Barely perceptible for 3 years. Recent progression	Onset after third thyroidectomy. Moderately advanced. Unchanged at present	Not done	Pre-op.-1 Postop.-1 Pre-op.-2 Postop.-2 Pre-op.-3 Postop.-3 Present	(+)50 (+)1 (+)45 (+)10 (+)49 (−)20 (+)5	Not done

Case Reports. Case 1. Q. A., a 57-year old white laborer, was admitted to the Veterans Hospital at Aspinwall on January 30, 1950, because of progressive protusion of the eyes for two months. Nervousness was ascribed to inability to sleep because of ocular burning. Prior to December, 1949, he had been able to read without difficulty and there had been no symptoms of thyrotoxicosis. The

past history revealed a burn of the left lower leg in 1915, a penile sore in 1918, and antisyphilitic therapy for 3 months in 1947. There was a previous admission in 1946 for bilateral nuclear cataracts but no mention was made of proptosis or thyroid disease at that time.

On physical examination there was no visible or palpable thyroid enlargement. Visual acuity was markedly diminished, especially on the left. There were considerable redness and edema of the eyelids. The bulbar and palpebral conjunctivae were injected and slightly chemotic. Proptosis measured 28 mm. on the right, 24 mm. on the left. Extraocular movements were limited and lagophthalmos was present on the left. Intraorbital tension was normal but with posterior pressure the eyeballs seemed set in a firm base.

The heart was enlarged to the left and the peripheral pulses were bounding. The pulse rate was 90, the blood pressure 180/90. Aortic systolic and diastolic murmurs were present.

Over the anterolateral aspect of each leg were pinkish, elevated, indurated, non-pitting, hairless, asymptomatic plaques. On the left, dilated hair follicles gave the skin a typical pigskin appearance.

Blood serology tests were doubtful. The serum cholesterol was 322 mg. per 100 cc.; fasting blood sugar 77 mg. per 100 cc. Roentgen-ray examination of the chest and skull showed nothing remarkable and a determination of the basal metabolic rate(BMR) was unsatisfactory.

Several ophthalmologists advised that immediate measures be instituted to relieve the proptosis, perferably orbital decompression. Accordingly, on February 6, a right frontal craniotomy was performed with removal of the bones of the right orbital roof and optic foramen (Naffziger procedure). On February 17 a left Naffziger procedure was done with removal of some fatty orbital tissue.

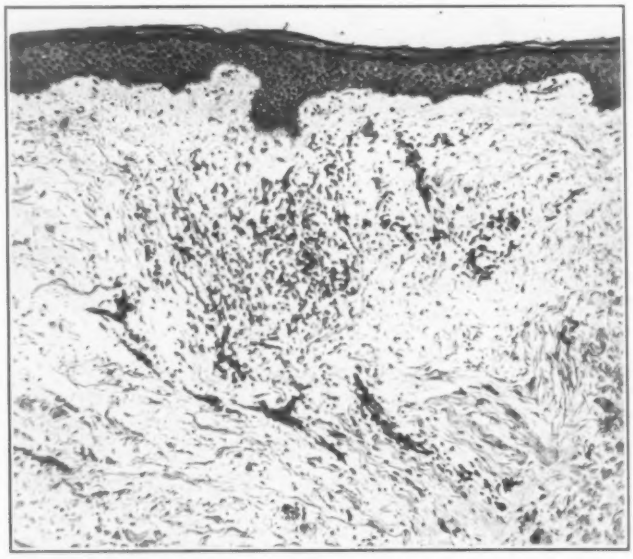

FIG. 1.—Case 1, skin biopsy. Diffuse myxomatous degeneration of collagen with cellular infiltration. Epidermis shows mild hyperkeratosis and atrophy.

Bilateral skin biopsies were reported as typical of moderately advanced localized myxedema (Fig. 1). These areas were bloodless and a colorless, sticky, gelatinous substance oozed from the incision for 2 days. The specimen of orbital fat was histologically normal.

After convalescence, 1 month following admission, further laboratory studies revealed: serum cholesterol 382 mg. per 100 cc.; BMR + 23% and + 20%; glucose tolerance test, fasting 91 mg. per 100 cc., ½ hour 185 mg. per 100 cc., 1 hour 237 mg. per 100 cc., 2 hours 270 mg. per 100 cc., 3 hours 238 mg. per 100 cc.; serum protein-bound

iodine, 6.5 gamma; 24-hour urinary 17-ketosteroids, 7.5 mg.

By March the proptosis had decreased to 25 mm. on the right and 22 mm. on the left. Desiccated thyroid, 1 grain daily, and Lugol's solution, 10 drops 3 times daily, were started. Hyaluronidase injections through the upper and lower lids were followed by a definite softening of the eyelids and seemingly of the retro-orbital tissues. However, this effect was transitory and in 24 hours the retro-orbital firmness and solid edema of the lid had returned to their pre-injection state.

Thirty minutes after diffuse subcutaneous injection of 300 turbidity units of hyaluronidase into the pretibial plaques, there was no evidence of softening or pitting. Ace bandages were immediately applied and 24 hours later most of the edema had been absorbed. The bandages were reapplied for 2 weeks, after which the marked improvement in the plaques was maintained up to the time of discharge.

On April 8 the patient developed symptoms of pneumonia with Roentgen-ray findings of consolidation of the right middle lobe. There was marked burning of both eyes with pronounced increase in the chemosis, a beefy red injection of the conjunctivae, and bilateral seropurulent discharge (Fig. 2). Neither eyelid could be closed and exophthalmometer readings were: right, 27 mm.; left, 30 mm. The pneumonic process responded immediately to antibiotics but no improvement was noted in the eyes. The dosage of desiccated thyroid was progressively increased to 4.5 grains daily.

A right corneal ulcer developed on April 13 which became widespread in 4 days while chemosis practically enveloped the eye. Pituitary irradiation was instituted on April 14 with 1500 Roentgen units in air to the left and right sides over a period of 2 weeks. On April 17 a left tarsorrhaphy was performed as an additional measure to attempt to prevent corneal ulceration on this side.

During the next two months the edema and conjunctival inflammation of the left eye progressively improved but the exophthalmometric readings remained unchanged. The right eye could not be salvaged. On July 1 he went on leave from which he failed to return. He was recalled in November when examination revealed no marked change in the proptosis of the left eye. A prosthesis replaced the enucleated right eye. The improvement in the localized myxedema had been maintained.

FIG. 2.—Exophthalmos in Case 1 after onset of pneumonia.

COMMENT. This is a case of malignant exophthalmos associated with localized pretibial myxedema with no historical, clinical, or laboratory evidence of thyrotoxicosis; nor had a thyroidectomy been performed. The numerous therapeutic measures insti-

tuted apparently were of no avail, with the possible exception of pituitary irradiation. Local hyaluronidase injections followed by pressure bandages produced a well-maintained improvement in the pretibial lesions.

Case 2. R. D., a 25-year old white male millworker, was first admitted to the hospital in March, 1948, with classical symptoms of hyperthyroidism, including bilateral exophthalmos and diffuse enlargement of the thyroid gland. The basal metabolic rate (BMR) was + 77% and the serum cholesterol 160 mg. per 100 cc. A subtotal thyroidectomy was performed in April following preparation with propylthiouracil and Lugol's solution. Convalescence was uneventful but there was no definite change in the exophthalmos postoperatively. For the next 6 months he was asymptomatic and the BMR was normal.

In July, 1950, he noted polyuria, polydipsia, and polyphagia together with a 30-pound loss of weight. Weakness, increased sweating, and heat intolerance had reappeared. The family history was negative for diabetes and thyroid diseases. On readmission in August, 1950, the physical examination revealed bilateral exophthalmos but no chemosis or edema of the lids. In contrast to Cases 1 and 3, there was no impression of a ligneous base on posterior pressure on the eyeballs. The thyroid gland was diffusely enlarged, the skin warm and moist, and there was a fine tremor of the hands. The pulse rate averaged 90 to 100 and the blood pressure was 125/60. Small areas of thickening of the skin over the anterolateral surfaces of both lower legs were palpable but barely visible. The BMR was + 38%, the serum cholesterol 239 mg. per 100 cc., serum protein-bound iodine was 10.2 gamma and the blood sugar 176 mg. per 100 cc. A skin biopsy from the left leg revealed early changes of localized myxedema (Fig 3).

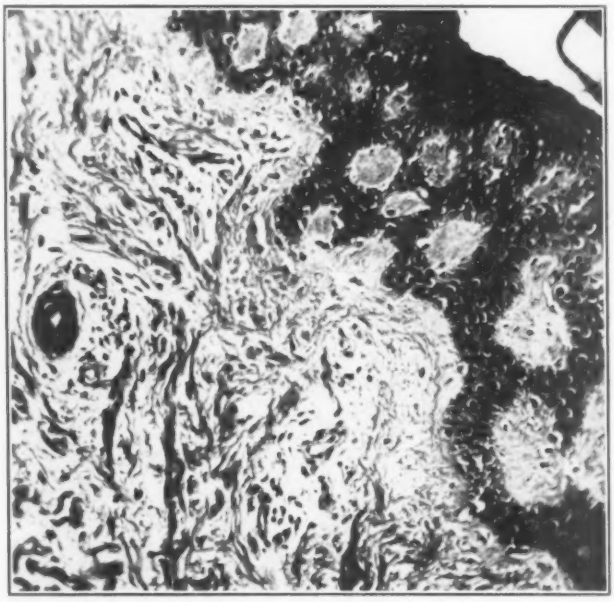

Fig. 3.—Case 2, skin biopsy. Early changes of localized myxedema including perivascular infiltration, areas of degeneration of collagen, and stellate cells in upper corium.

Following admission the diabetes was controlled with a diabetic diet of 2500 calories and 48 units of insulin "21." Propylthiouracil therapy, 300 mg. daily in 4 divided doses, was begun. The symptoms of thyrotoxicosis improved and the patient gained 12 pounds. Frequent exophthalmometric readings revealed no change in the exophthalmos. The skin lesions became more obvious a month after admission, following which they grad-

ually regressed. The response of the pituitary to epinephrine, as measured by a fall in circulating eosinophils, was normal. The 17-ketosteroid excretion determined on a 24-hour urine collection was 8.3 mg.

COMMENT. This case was one of clear-cut thyrotoxicosis with nonmalignant exophthalmos until thyroidectomy was performed. This was followed by the development of early localized pretibial myxedema, recurrence of thyrotoxicosis, and onset of diabetes mellitus, but no obvious progression of the exophthalmos. Treatment with propylthiouracil has thus far resulted in control of the thyrotoxicosis without a deleterious effect on the exophthalmos or localized myxedema. Careful supervision of the patient will certainly be necessary for several years before definite conclusions may be drawn. However, it is interesting to speculate on the relationship of possible pituitary overactivity and the development of permanent diabetes mellitus. This is especially true since in Case 1 the glucose tolerance curve was shown to be definitely diabetic although clinical diabetes was not present.

CASE 3. H. P., a 37-year old white male truckdriver, first noted symptoms of thyrotoxicosis in September, 1948. These included nervousness, loss of weight, and marked protrusion of the left eye. In February, 1949, after preparation for 10 days with Lugol's solution, a subtotal thyroidectomy was performed at another hospital. Following operation the left eye became much less prominent. However, symptoms of hypothyroidism became evident and he was placed on 2 grains of desiccated thyroid daily. In January, 1950, 8 months before his present admission, progressive protrusion of the right eye was noted along with diplopia and swelling of the skin over the anterolateral aspect of both lower legs. On admission to the hospital in September, 1950, his only complaints were referable to his eyes. He had continued taking thyroid extract, 0.5 to 2.0 grains daily. The family

FIG. 4.—Exophthalmos in Case 3. Note ocular muscle imbalance.

history revealed that 1 brother had been rejected for military service because of nervousness and protruding eyes.

Physical examination revealed marked bilateral exophthalmos (Fig. 4), greater on the left, with periorbital swelling, scleral injection, imbalance of the ocular muscles and edema of both upper and lower lids. Lagophthalmos was not present but posterior pressure on the eyeballs imparted a ligneous sensation. Well-circumscribed, waxy, nonpitting, plaque-like areas of indurated skin were obvious over the lower third of the anterolateral aspect of both legs. There were no signs of thyrotoxicosis nor was the thyroid gland palpable. Laboratory studies revealed a BMR of — 6%, serum cholesterol 218 mg. per 100 cc., and serum protein-bound iodine 6.2 gamma. A biopsy from one of the leg plaques showed moderately advanced localized myxedema (Fig. 5).

Following admission, the dosage of desiccated thyroid was gradually increased to 4.5 grains daily. After 5 weeks the BMR was + 11%. The eyes had improved both subjectively and objectively. Less tearing, inflammation, and puffiness of the lids were present. An insulin tolerance test using 7 units of crystalline zinc-insulin was reported as follows: fasting 70 mg. per 100 cc.; 15 minutes, 44 mg. per 100 cc.; 30 minutes, 62 mg. per 100 cc.; 45 minutes, 43 mg. per 100 cc.; 90 minutes, 30 mg. per 100 cc. The test was terminated because of continued symptoms of insulin shock. The 24-hour urinary 17-ketosteroids were 14.4 mg. An eosinophil count was 220 per cu. mm., and 4 hours after injection of 0.3 cc. of epinephrine 1:1000 the eosinophils numbered 66 per cu. mm.

After 6 weeks of hospitalization the patient went home on a 30-day furlough. During this time he took 4.5 grains of desiccated thyroid daily with no further symptoms of hyperthyroidism except excess sweating. On returning, he volunteered the information that all excess tearing had ceased and that diplopia had almost disappeared. The conjunctivae were less congested and lid edema was no longer present. Exophthalmometric readings had decreased 3 mm. in the right eye and 2 mm. in the left eye. The pulse rate was 88 and the hands were moist and warm. The greatest change was in the localized pretibial myxedema which had regressed markedly. Although the lesions were still vis-

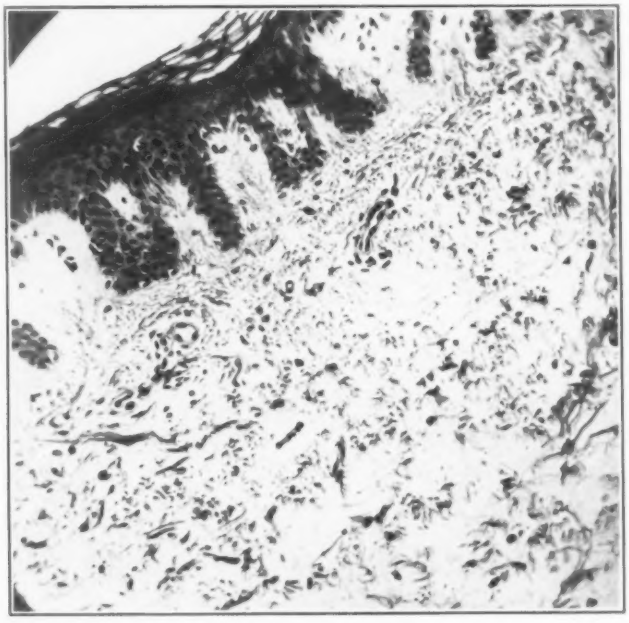

FIG. 5.—Case 3, skin biopsy. Area showing hyperkeratosis, many stellate cells, "teased tissue", and mild perivascular infiltration.

ible they were softer, smaller, and less sharply demarcated. He was discharged to continue on 4.5 grains of desiccated thyroid daily.

COMMENT. From the onset of symptoms this patient showed signs of a malignant exophthalmos. Postoperatively, he developed symptoms of hypothyroidism consisting of intolerance to cold, listlessness, loss of scalp hair, and hypotension. The impression is that his leg and eye lesions improved with larger doses of desiccated thyroid. Continued close supervision will be necessary. Here the pattern was that of exophthalmos progressing 1 year after operation, with the onset of localized myxedema coinciding with the advancing proptosis.

CASE 4. L. M., a 27-year old white male, a mechanical engineer, developed symptoms of thyrotoxicosis in February, 1945, approximately 7 months following his induction into the service. The past history and family history were not remarkable. The basal metabolic rate (BMR) varied from + 30 to + 50% but exophthalmos was not evident. Because of operative complications only a right hemithyroidectomy could be completed. Two months postorperatively he developed a recurrence of the hyperthyroidism with the BMR becoming elevated to + 40%. He was then given Lugol's solution and propylthiouracil for 5 weeks before his second operation which consisted of excision of approximately 90% of the left lobe in addition to the isthmus.

Following convalescence, the patient was separated from the service in June, 1946. At this time his BMR varied from + 10% to + 15%. Six months later symptoms of thyrotoxicosis again recurred and in February, 1947, his BMR was + 49%, while his pulse

FIG. 6.—Localized pretibial myedema, Case 4. Arrows denote lesions.

rate was 126 per minute. An examiner noted early exophthalmos for the first time. After preparation with Lugol's solution and propylthiouracil, a 3rd thyroidectomy was performed in May, 1947. The BMR postoperatively fell to — 20%.

During July and August, 1947, he noticed the presence of erythema on the anterolateral aspects of both lower legs, although there was no elevation or edema noted at this time. In October, 1947, the BMR was + 9% but during November and December of 1947 it varied from + 30% to + 40%. He was placed on 200 mg. of propylthiouracil daily in divided doses until May, 1948, when the dosage was dropped to 50 mg. daily. The BMR dropped to — 18% while the weight and pulse became stabilized. The lesions on both lower legs gradually increased in size and became elevated. They showed a thickened, leather-like, purplish red skin associated with non-pitting edema (Fig. 6).

During 1949 he was seen at regular intervals by one of us (F.T.H.). There was no change in the appearance of the skin lesions and no apparent progression of the exophthalmos. Propylthiouracil was discontinued in January, 1950, after he had been euthyroid for at least a year. At this time a biopsy of the lesion of the right leg was reported to show moderately advanced localized myxedema (Fig. 7).

During the past seven months the exophthalmos has gradually increased. BMR readings have continued to be normal and there has been no evidence of thyrotoxicosis. Exophthalmometric readings were 18 mm. in the right eye and 19 mm. in the left. Potassium iodide was started and therapy with desiccated thyroid is contemplated.

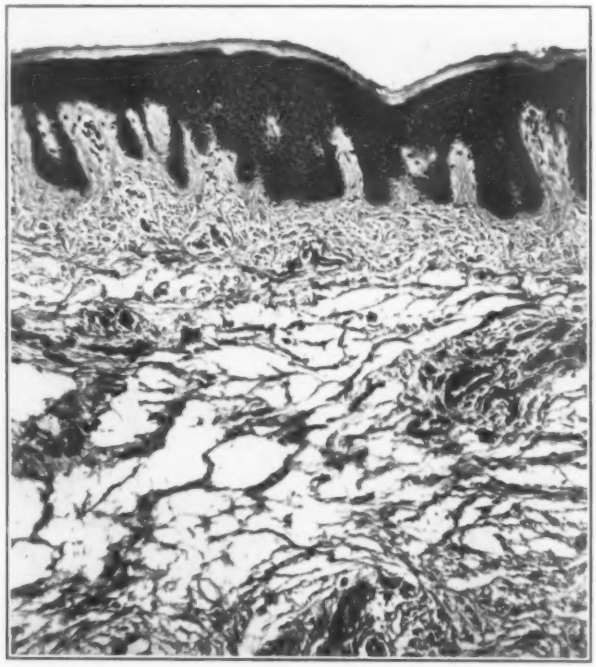

FIG. 7.—Case 4, skin biopsy. In the upper corium is a band of myxomatous degeneration of collagen with many stellate cells and basophilic degeneration of remaining strands. There is mild hyperkeratosis and typical "teased tissue".

COMMENT. In this case exophthalmos did not develop until late in the course of the disease, just prior to the 3rd thyroidectomy in 1947. This remained barely discernible until 1950, when progression became more rapid. Presumably, the excess of thyrotropic

hormone, in the absence of thyroid inhibition, has been responsible for this late rapid change. In view of the improvement with thyroid extract noted in Case 3, it will be interesting to observe the progress under thyroid medication in this case. It should also be pointed out that the localized pretibial myxedema followed a fall in BMR from + 49% to — 20% following the last thyroidectomy.

Discussion. The exophthalmos of Graves's disease is generally suspected to be due to the action of a hormone produced by the anterior lobe of the pituitary gland. Whether this hormone is the thyrotropic hormone, or some other pituitary factor, is as yet uncertain[3,5].

It has been postulated that localized myxedema is likely to develop when thyrotropic hormone is produced in relative or absolute excess. This situation theoretically occurs after thyroidectomy, with anti-thyroid drugs, or, if for any other reason, the thyroid is unable to respond to thyrotropic stimulation. Under these conditions sufficient thyroxin cannot be produced to inhibit the production of pituitary thyrotropic hormone. Cases 2, 3, and 4 fit into the post-thyroidectomy category. It may be noted that in all 3 of these patients the development of localized myxedema followed a rather precipitous fall in the metabolic rate. Other authors[11,12] have noted that localized myxedema occurs most commonly, but not exclusively, after thyroidectomy, particularly with recurrent thyrotoxicosis. Case 2 was hyperthyroid, Case 3 hypothyroid, and Cases 1 and 4 presumably euthyroid when the localized myxedema first appeared.

The fact that localized myxedema never occurs in the absence of exophthalmos is in harmony with the theory that the same hormonal imbalance produces both lesions[1]. However, exophthalmos without concomitant or subsequent development of localized myxedema is common. This suggests either that the hormone must act for a longer time to produce the cutaneous lesion, or that some additional factor is necessary for the development of localized myxedema. In the patients in this series there was presumption of unusually marked anterior pituitary activity (progressive exophthalmos in Cases 1 and 3 and probably 4; recurrent thyrotoxicosis in Cases 2 and 4). In Cases 1 there was very little response by the thyroid to thyrotropic stimulation. Curtis[2], in a personal communication, has suggested that this patient may have developed spontaneous exhaustion of the thyroid.

Treatment of localized myxedema itself is usually unnecessary since the lesion seldom troubles the patient. Moreover, several authors have noted spontaneous remissions after months or years without change in thyroid status[4,16]. In Case 1 injection of hyaluronidase and application of pressure bandages as recommended by Mills and Forsey[9] were followed by improvement. Injection of hyaluronidase retrobulbarly and into the lids has been suggested in the treatment of progressive exophthalmos[7]. In the patient in this study the injection of hyaluronidase into 1 eye produced no objective improvement but occasioned considerable pain, presumably due to the pressure bandage. Kadin[6] has reported 1 case in which hyaluronidase increased the edema and proptosis.

A review of the literature reveals that a uniformly satisfactory management of progressive exophthalmos, with or without thyrotoxicosis, has not been attained. Treatment has included one or a combination of the following: thyroidectomy, antithyroid drugs, desiccated thyroid, iodine, estrogenic substances, diuretics, irradiation of the

pituitary gland, cauterization of the pituitary gland, and retro-orbital hyaluronidase injections. When, ultimately, the point is reached where tarsorrhaphy, surgical decompression, or both are required, the case becomes a therapeutic failure. The evaluation of therapy is hampered by our knowledge that the proptosis may remain stationary at any particular stage and may even spontaneously regress. The reasons for this remain unknown and the same nebulous aura surrounds the localized myxedema. Almost the gamut of itemized therapy was given in Case 1. When last seen this patient showed slight improvement in the 1 remaining eye but this cannot justifiably be attributed to the pituitary irradiation. In Case 2, following administration of propylthiouracil, there were almost complete disappearance of the leg lesions and notable improvement in the hyperthyroid state, but no change in diabetic or exophthalmic status. This response is not consistent with the concepts of the pituitary–thyroid axis. Should he subsequently develop an increase in the proptosis, it would serve to confirm Curtis' view that localized myxedema is a contraindication to the use of anti-thyroid drugs. A better understanding of the differentiation bebetween thyrotoxic and thyrotropic exophthalmos may be necessary before more rational therapy can be anticipated[10]. In contrast, Case 3, treated with desiccated thyroid alone, showed a favorable subjective and objective response in the eyes and legs, thus conforming to the pituitary–thyroid theory. In Case 4 mild exophthalmos developed prior to the 3rd thyroidectomy for recurrent thyrotoxicosis. Now, 3 years later, the increasing proptosis warrants therapy with desiccated thyroid.

In the first 3 cases an attempt to evaluate other pituitary derangements has been made. The findings include: a diabetic glucose tolerance curve in Case 1; the development after thyroidectomy of frank diabetes in Case 2; an insulin tolerance curve while on desiccated thyroid suggesting hypopituitarism in Case 3; normal response of the circulating eosinophils to epinephrine and adrenocorticotropic hormone in Cases 2 and 3; normal 17-ketosteroids in all 3 cases.

Summary and Conclusions. 1. Four patients with localized myxedema associated with exophthalmos are presented.

2. One of these is believed to be the first reported case presenting the combined lesions of localized myxedema and progressive exophthalmos without having had previous thyrotoxicosis or thyroidectomy.

3. The fact that the localized myxedema was associated with progressive exophthalmos in 3 cases suggests that the leg lesion may be used as a danger signal which presages a progression of the proptosis.

4. Localized myxedema may occur in hyperthyroid, hypothyroid, or euthyroid states.

5. The concept of the pituitary-thyroid axis was not directly applicable to all these cases. Further experience with the syndrome will undoubtedly modify this theory.

6. The authors' experience indicates that localized myxedema associated with exophthalmos is not too rare a syndrome. Increasing clinical awareness of the possible coexistence of these lesions should unearth a greater incidence. A sounder therapeutic regimen may eventuate from this increasing recognition.

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RE-FEEDING (NUTRITIONAL) GYNECOMASTIA IN CIRRHOSIS OF THE LIVER: I. CLINICAL OBSERVATIONS*†

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In 1944 and 1945 one of us (R.M.K.) observed the appearance of gynecomastia with associated orchitis in liberated prisoners of war seen in North Africa and the Far East[18]. These bizarre signs appeared in soldiers *after* re-feeding and rehabilitation had begun to restore their severely wasted tissues. Gynecomastia has also been observed in cirrhosis of the liver and has been considered an evidence of hepatic insufficiency. We here report the observation in cirrhotic patients of the re-feeding type of gynecomastia as well as that due to hepatic insufficiency.

In 1945 Musselman[15] first described what is now called nutritional gynecomastia, but which the authors believe should be more correctly named "re-feeding" or "rehabilitation" gynecomastia. The reason for suggesting these new names for the syndrome is that, as far as we can ascertain, no one has reported the appearance of this type of gynecomastia in man or in male animals *during* the development or progression of natural or induced malnutrition. Musselman was an Army medical officer, a prisoner of war in Cabanatuan, and he gave a vivid and graphic description of the waxing and waning of a wide variety of malnutrition syndromes among American soldiers held by the Japanese in the Philippines. In his paper, he reported that in the beginning of 1943, Red Cross food parcels first appeared in the prisoner-of-war camp where he was held captive. His recorded observations were:

> Following the increase in diet, with resolution of deficiency symptoms and improvement in the general health of the men, a peculiar phenomenon occurred. An increasing number of men came in complaining of tender lumps beneath their nipples. A smooth firm tender mass, loosely fixed to the nipple but freely movable over the deep structures, appeared and gradually grew to a size as large as 2.5 cm. in diameter. A milk-like fluid could sometimes be expressed from the nipple by pressure on the mass. After being present for 1 to 3 months these masses gradually subsided in a similar length of time. These breast "tumors" occurred in no particular physical type of man. The history revealed no pertinent facts except the suggestion of an

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† The opinions expressed in this paper are those of the authors and do not necessarily represent the official views of any governmental agency.

increase in libido as expressed by an increase in the frequency of erection and nocturnal emissions. A few of these "tumors" were excised. On section of the button-like mass the macroscopic appearance was similar to that of a fibroadenoma of the breast. It appears possible that these changes were similar to the temporary congestion and inflammation seen in the male breast at puberty. At the same time a number of men had slight enlargement and tenderness of one or both testicles. No fever, prostatitis or urethritis was associated with these changes.

By June of 1943 the Red Cross food parcels were exhausted and the men returned to their former miserable state of severe inanition and deficiency. In December of 1943 a second shipment of Red Cross food arrived:

> Again general health and nutrition improved and symptoms subsided. Again a number of so-called breast tumors appeared, increased in size and resolved. Some men showed changes in the testes similar to those which had appeared a year before.

In 1946 and 1947, Klatskin and his colleagues[12,19,20] published detailed clinical, histologic, and biochemical studies of a group of soldiers, prisoners of the Japanese in the Philippines, 16% of whom developed gynecomastia after liberation and re-feeding. These men were first examined some months after being set free and the clinical and histologic studies confirmed and extended Musselman's observations. Klatskin found decreased spermatogenesis, but made no note of orchitis, in his patients.

Biochemical studies made on urine from the soldiers showed that excretion of 17-ketosteriods was slightly low and that urinary estrogens were within normal limits. Free estrogen was not found in the urine.

Two Types of Gynecomastia in Cirrhosis. In cirrhosis the appearance of gynecomastia[5] is usually considered to be evidence of severe hepatic insufficiency and under these circumstances is a herald of decline. It is associated clinically with increasing malnutrition, with testicular atrophy, spider nevi, loss of libido, loss of potency, infertility, torso alopecia, prostatic atrophy, palmar erythema and with impaired liver function tests[2,3,8,13]. The pathophysiological explanation of the "demasculinization" is that the damaged liver is unable to detoxify circulating estrogen and that, with increased blood levels of this hormone in the blood, target organs are feminized[8].

While this type of gynecomastia is fairly common, its exact incidence among cirrhotics is not known. It has been reported[13] to occur in up to 40% of cirrhotic patients, but in the authors' experience these figures are very high. However, the development, clinical course, and biochemistry constitute a distinct syndrome which is quite unlike the re-feeding gynecomastia of soldiers.

In the past 3 years, 9 male alcoholic patients ill with cirrhosis and marked tissue wasting have been observed who developed gynecomastia during rehabilitation with diets high in protein and high in calories. This gynecomastia syndrome is quite different from the one seen in patients severely ill with cirrhosis and described above, and we believe it to be identical with the gynecomastia syndrome observed in rehabilitated soldiers.

When first seen, these 9 alcoholic cirrhotics had ascites or edema and in them tissue wasting was obvious. Seven of the 9 were feminized. Hair was absent from the chest, they showed a female pubic escutcheon, and libido was absent or markedly diminished. The remaining 2 patients were extremely hairy men, but both had lost libido. No gynecomastia was evident by palpation in any of these men at

the time of admission and in 5 the testicles were small. In all patients liver function tests were disturbed and typical of advanced cirrhosis. Prolonged diet therapy successfully restored tissue mass in all these patients and liver function tests, especially serum cholinesterase levels[21], returned toward normal values.

Four of the patients were observed during metabolic balance studies and in each patient, after an initial period of negative nitrogen balance, a strongly positive nitrogen balance developed with high protein feedings. This positive nitrogen balance was prolonged, its appearance antedated the gynecomastia, and it was associated with a small but steady diuresis. In all instances gain in weight and return of libido preceded appearance of gynecomastia. In the 5 patients with small testes, these enlarged somewhat before gynecomastia was maximum and in 2 patients the testicles were more tender than usual. In one of the men considered to have normal sized testicles on admission there was some enlargement with tenderness during the period of rehabilitation. In none of these patients was the orchitis as marked as seen in some prisoners of war who developed swelling of the testes during re-feeding gynecomastia.

Breast enlargement with tenderness was first noted from 18 days to 4 months after the beginning of rehabilitation and in 1 patient it did not disappear for as long as 5 months after its development. The gynecomastia was unilateral and small in 1 patient and in the others it was bilateral and ranged in size from largish nodular breasts 4 inches across to a small firm flat knobby 1-inch disc of tissue under the areola. No secretion could be expressed from the breasts.

At the time of the appearance of the gynecomastia, but usually thereafter, fine silken hairs began to grow on the chest and above the pubis. Axillary hair growth was vigorous and 2 patients stated spontaneously that they had to shave more often than previously. In 5 patients with ascites the appearance of gynecomastia did not have any gross effect on the rate of accumulation of ascitic fluid even though a relative diuresis was noted.

Below is recorded a case history of 1 of the 4 patients with gynecomastia who were studied in some detail, by means of metabolic balances.

Case Report. A. M., a 32-year-old single veteran, had been drinking alcohol to excess from the time he was 17 years old. From 1942 to 1946 he served in the Army but was never overseas. He was discharged because of "psychoneurosis." He then worked in Chicago as a laborer, drinking heavily and living on an unbalanced dietary intake.

In December, 1946, he first became jaundiced and his legs were found to be edematous up to, and including, the scrotum. There was also slight ascites. A diagnosis of alcoholism and cirrhosis was entertained at this time and he was admitted to a Veterans' Hospital. He was in the hospital for 6 months and during this time responded well to a regimen of bed rest and diet therapy. On discharge from the hospital he returned to his former habits and was admitted a second time in September, 1947, for 3 months' care. In April, 1948, he vomited a pint of blood and was again admitted to the Veterans' Hospital where he was found to have ascites but no jaundice. After 6 weeks in the hospital he was discharged but continued his drinking and had a second hematemesis in June, 1948, when he was admitted to Cook County Hospital. There was some ascitic fluid but this disappeared after transfusions and with bed rest. In August he was admitted to the Research and Educational Hospitals of the University of Illinois for metabolic studies, details of which are being published elsewhere (Fig. 1).

On admission (Fig. 1A) he was well developed, but obvious inanition was present, his weight being 70 kg. He was icteric, pale, with a fine silky skin, female pubic hair, and absent to scanty hair in the axillae, on the chest, and on the extremities. There was increased vasularity over the abdomen and 12 telangectases were counted on his body. Ascitic fluid was not detected, the liver was

grossly enlarged, firm, smooth, and not tender. The spleen was not enlarged. His testicles were small but not tender or painful. His penis was of normal size. Edema of both ankles was present and decubitus ulcers were found on his left leg and sacral area. On direct questioning he stated that there had been loss of libido for at least a year. The rest of the physical examination was not striking. There was no evidence of specific vitamin deficiency syndromes. The blood pressure was low (95/65), the pulse 62, the temperature normal.

LABORATORY AND SPECIAL EXAMINATIONS. Radiographic studies of the chest and entire gastrointestinal tract showed no abnormalities. However, some osteoporosis of the long bones of the legs was seen. The electrocardiograph showed sinus bradycardia with low voltage throughout. It was interpreted by Dr. I. R. Callen as showing the results of edema or obesity. Urinalysis showed a specific gravity of 1021, and pH 6.0. Gross bilirubinuria was present. No other abnormalities were found either by macroscopic or microscopic examination. The hematocrit was 35%, the hemoglobin 11.0 gm. per 100 cc., the red blood cell count 3.5 million per c.mm., the white cell count 8,700. The differential count was within normal limits. The reticulocyte count was 0.05%. Bone marrow biopsy showed changes consistent with liver disease. Nonprotein nitrogen was 32 mg. per 100 cc., albumin 3.9 gm., and globulin 2.7 gm. The serum cholinesterase was 0.52 △ pH per hr. Bromsulphalein retention was 39%, 45 minutes after injection of the dye. The "1 minute" bilirubin was 0.7 mg. per 100 cc. and the total bilirubin was 1.7 mg. The urinary urobilinogen was 0.64 Ehrlich unit. Cephalin flocculation was 1 + unit. Thymol turbidity was 5 Maclagan units. Thymol flocculation was 3 + units. Diagnoses were made of alcoholism and cirrhosis of the liver, with feminization, decubitus ulcers, anemia of cirrhosis, and edema.

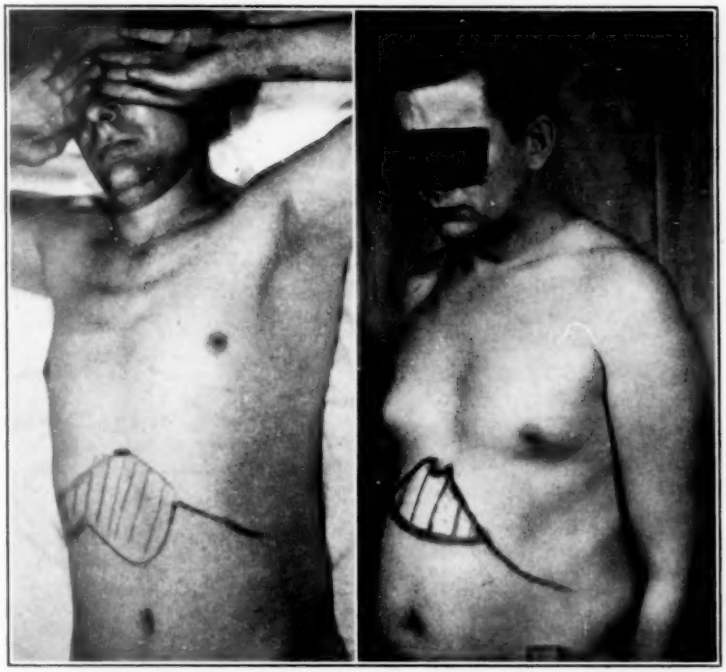

FIG. 1.—Photographs of patient A. M. ill with cirrhosis taken soon after admission (A, left) and at height of re-feeding gynecomastia (B, right). Note gain in body mass, reduction of liver size (indicated by pencilled abdominal surface markings), and large breasts. Increased hair growth was present at this time but cannot be seen on the photograph. The left hand photograph shows absence of axillary hair.

When all the diagnostic procedures were completed the patient was studied in an air-conditioned metabolic unit where a 126-day metabolic study was carried out. During this time he was up and about and consumed a diet which provided each day 2.5 gm. of protein per kg. of body weight and twice the basal requirements for calories (30% of the total calories as fat and the remainder of the calories as carbohydrate.) The sodium content of the diet was kept below 0.9 gm. per day. Fluid intake (including all beverages) was kept constant at 2.5 liters per day. The diet was supplemented on one occasion with 120 gm. of amino acid preparation per day for 18 days and with 50 gm. of serum albumin a day for a 2nd period of 18 days. Complete routine examinations and clinical laboratory procedures were made at least once a week. Photographs of the patient were taken every 18 days. Serial changes in nitrogen balance, fluid balance, body weight, and serum cholinesterase activity are shown in Fig. 2.

During the first 18 days of the study the ankle edema disappeared completely. On the 18th day the left breast became tender and slightly enlarged. From that time on both breasts enlarged considerably and became tender, and glandular tissue was easily palpable. The enlargement progressed until the 51st day of the study; thereafter the breasts became less tender, less hard to the touch and decreased in size, the changes disappearing completely 5 months after they first appeared. Concomitant with the appearance of the breast enlargement, morning erections and return of libido were reported. The testes were slightly tender and gradually enlarged to normal size. Nocturnal emissions occurred

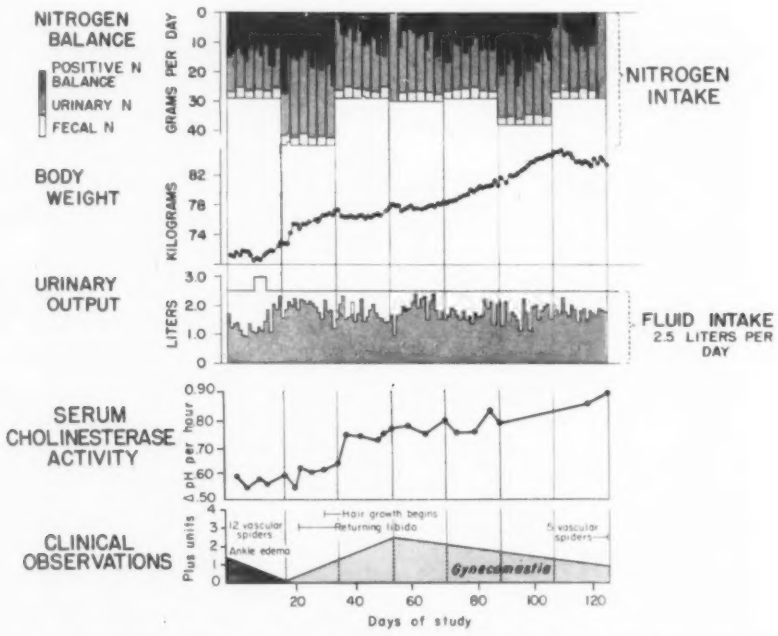

FIG. 2.—The effects of 3 months' therapy with a diet low in sodium (33 mEq. per day), high in protein (from 181 to 306 gm. of protein per day) and calories, together with a fixed fluid intake (2.5 liters per day) on the nitrogen balance, body weight, urinary output, and serum cholinesterase in patient A. M., ill with cirrhosis and tissue depletion, who developed re-feeding gynecomastia during recovery and remasculinization. Note (a) long-continued markedly positive nitrogen balance; (b) steady increase in body weight after initial lag; (c) long-continued diuresis beginning during the 3rd week of therapy; (d) increase of serum cholinesterase, especially at the 5th week; (e) disappearance of edema and beginning of remasculinization after 3 weeks of therapy. Maximum gynecomastia seen at end of 7 weeks of therapy.

during the 3rd month of the study, these being the 1st ejaculations which he noticed for over 18 months. There was no discernible hair growth on patient A. M.'s chest on admission. By the 23rd day, 20 fine hairs, up to ¼ inch in length, were noted on the anterior chest wall. By the 69th day, hair growth was marked on chest, nipples, legs, feet, pubis and axillae. The patient spontaneously volunteered that the hair on his head had ceased falling out, although previously he had lost noticeable amounts when combing or washing his hair. During the first 10 days of the study the enlarged liver showed considerable reduction in size, especially in the right lobe. During the remainder of the study gradual reduction in liver size continued until, at the time of discharge, the liver could not be palpated. The impaired liver function tests returned slowly to normal. Bilirubinuria disappeared by the 10th day. The only rapid changes were serum cholinesterase activity which climbed rapidly from the 18th day onward. At discharge the "1 minute" bilirubin was 0.05 mg., the total bilirubin 0.2 mg., the bromsulfalein retention 23% at 45 minutes, the thymol turbidity 2 Maclagan units, the thymol flocculation 1 + unit, and the cephalin flocculation zero unit. The urinary urobilinogen was 0.4 Ehrlich unit. The hematocrit was 35%, hemoglobin 11.4 gm., red blood cells 3.3 million, and white blood cells 4,500.

Clinical improvement was striking, both physically and psychologically. Seven months after beginning the regimen the patient was completely well. He has continued to remain in good health during the past 2 years and, as yet, remains a teetotaler.

Comment. From a clinical standpoint and as judged by nitrogen retention and serum cholinesterase activity, the greatest improvement in this patient occurred during the first 36 days of the study. During this time his nutrition improved, diuresis began, he lost his jaundice and edema, his enlarged liver regressed, he began to regain his masculinity and also his breasts started to develop. The fact that the gynecomastia began at a time when masculinity reappeared and at a time when liver function was obviously improving, as judged by loss of jaundice, decrease in liver size, and rapid rise in serum cholinesterase activity[21], is very strong evidence in this instance against the concept that the gynecomastia developed because the liver was unable to detoxify circulating estrogens. On the other hand, the temporal relationship between rapidly improving nutrition and the development of the breasts is extremely suggestive of re-feeding gynecomastia, as seen in liberated prisoners of war.

The markedly positive nitrogen balance throughout the study is indicative of a striking capacity to lay down protoplasm, as shown by gain in body weight. If one calculates the hypothetical gain in weight on the basis of nitrogen retention, the increase in body weight is much less than that which would have theoretically obtained, had the nitrogen been retained without changes in body water. To account for the less than theoretical gain in weight, it may be postulated that the tissues of this patient initially contained large amounts of fluid and relatively little protoplasm, and that throughout the study, this fluid was supplanted by newly synthesized tissue protein. The long-continued diuresis of water and potassium from the 16th to the 95th day is a point in favor of this hypothesis.

Discussion. Gynecomastia appearing during re-feeding and rehabilitation of the cirrhotic has been reported, briefly, by the authors[14] in 1949. At this time it is emphasized that this gynecomastia appears during the remasculinization of the patient and is different from the well-known feminizing gynecomastia syndrome of severely ill cirrhotic patients. The authors speculated that the mammogenic substance is liberated by the growth of a starved and atrophied testis when it or the pituitary gland is liberally supplied with necessary nutrients. This mammogenic substance might be androgen, inhibin, or some other hormone[1]. It certainly is

not estrogen, which feminizes and which is anti-diuretic. Its effects bring to mind the gynecomastia syndrome produced by mammogenic testicular tumors[4].

Klatskin[12,19,20] and others have suggested that the gynecomastia of rehabilitated soldiers is related to previous, or active, hepatic disease, but they could not find any direct evidence of impairment of liver function in their subjects. It is suprising that all reports of re-feeding (nutritional) gynecomastia in malnourished soldiers and civilians have come from tropical or semi-tropical areas[9,16,17]. Re-feeding gynecomastia has not been reported from other areas where famine, semi-starvation, and malnutrition have been observed. Because of this it has been suggested that simple caloric undernutrition could not have been the major or sole cause of the condition. While this may be true, it should be pointed out that gynecomastia was not reported in the 1943 Bengal famine[7] nor was it recognized and reported in Africa until recent years[6], although it is a very common physical abnormality in male African Negroes, if one takes the trouble to do examinations of their breasts. Thus a slight possibility exists that re-feeding gynecomastia was overlooked when starving European populations were rehabilitated. Since long-continued negative nitrogen balance is a common finding in alcoholism and alcoholic cirrhosis of the liver[10], it is possible that arginine, which is an essential amino acid for normal spermatogenesis, may be the nutrient which the nutritionally bankrupt cirrhotic requires to restore his masculinity. Attempts to prove this hypothesis have so far been unsuccessful.

Summary. 1. Re-feeding (nutritional) gynecomastia was noted in 9 male patients ill with alcoholism, cirrhosis of the liver, and inanition.

2. The transitory breast enlargements developed during rehabilitation and recovery from cirrhosis during a high-protein dietary regimen. It is different from the usual type of gynecomastia seen in cirrhosis, which is associated with feminization of the male and poor liver function.

3. Re-feeding gynecomastia appeared during remasculinization of the feminized cirrhotic and was associated with a prolonged positive nitrogen balance, gain in weight, slight testicular swelling, regrowth of male hair, improvement of liver function, and return of male libido.

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PULMONARY CIRCULATION TIMES WITH PARTICULAR RELATIONSHIP TO ACUTE HYPOXIA

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During an investigation of the cardiovascular status of patients with neoplastic diseases, it became desirable to ascertain the velocities of the arterial and venous segments of the pulmonary circulation. It was necessary, therefore, to develop a technique for such determinations, since the methods previously described were not suitable for the particular problem under study.

A simple, objective method for determining right and left heart circulation time has been the aim of many investigators[1,2,8,12,21,22]. Objective methods have consistently shown more reliable results[10,15,16] than have subjective methods. Blumgart and his associates[1] introduced the use of radioactive material which, with modification, has been considered essentially the most accurate method for the past decade. Despite the rapid advancement and availability of radioactive material and detectors, the clinical application of the technique is impractical, at the present time, for most institutions or physicians. Furthermore, the hazard of excessive irradiation during repeated and frequent determinations is formidable.

As a readily repeatable procedure for obtaining multiple circulation times, a non-radioactive substance (methylene blue), oxygen and nitrogen inhalation, and the oximeter have been employed[11,17]. Similar methods[8,12] utilizing photoelectric cells have been reported but these do not detect oxyhemoglobin[13] or permit multiple determinations of velocity of pulmonary blood flow. The method described in this report employs the oximeter to detect both methylene blue and oxyhemoglobin. This method has been developed and studied in this laboratory for 4 years and is now considered sufficiently reliable and practical for clinical use.

Method. Thirty-two medical students and laboratory personnel, varying in age from 24 to 36, served as normal subjects. There was no history or physical finding of any circulatory, respiratory or hematological disorder in this group. Seventeen patients suffering from chronic diseases were studied repeatedly with both techniques.

The Millikan oximeter with an automatic compensating circuit was used to determine the arrival of oxyhemoglobin or methylene blue[13]. The oximeter detects and continuously measures the oxyhemoglobin saturation of the blood circulating through the ear. The compensating circuit automatically adjusts for minor changes in ear thickness, after the initial flushing of the ear. The oximeter readings were determined directly from a Rubicon galvanometer, the fluctuations being timed by a stopwatch with an accuracy of 0.02 second.

1. Lung-to-Ear Circulation Time (Left Heart Time). The oximeter was placed on the left ear after appropriate calibration with the "standard" ear. The ear vessels were allowed to warm for at least 20 to 40 minutes. When the oxygen saturation of arterial blood was not directly determined gasometrically, the subject was required to breathe 100% oxygen for at least 3 minutes and the oximeter was then set at 99.5%. Subsequently, the oximeter usually fell to between 95 and 97% (for the normal subjects) as soon as room air was again breathed, and this was taken as the arterial oxygen saturation[3].

Determinations around 95% saturation by oxygen inhalation[4] were found to be quite variable. Movements of the galvanometer due to oxygen or nitrogen inhalation at the 95% saturation level were small and slow, making for a poorly defined end-point. Galvanometer movements at lower oxygen saturation levels were sharper and more accurately discernible. Determinations at lower than 95% oxygen saturation were accomplished by having the subject inhale deeply of room air at a given signal, after breathing 100% nitrogen. Varying the depth or duration of inspiration did not significantly alter the findings. Inhalation of 100% nitrogen for about 30 seconds was sufficient to drop the oxygen saturation to 60% in most subjects. Breathing approximately 10% oxygen for periods of 2 to 5 minutes produced findings similar to the 30-second period of hypoxia.

The subjects were given from 3 to 10 practice trials to teach them the procedure. Normal respirations were taken during the nitrogen breathing period. As the galvanometer beam approached the desired oxygen saturation, the subject was told to expire normally and then to hold his breath and remove the mask. Shortly thereafter, at a given signal, the subject was told to take a short, rapid, deep inspiration of room air. The stop watch was started at the moment the inspiration was taken and stopped at the first upward movement of the galvanometer; the saturation at this point was recorded.

Most determinations were checked 3 times during each test. Circulation times were recorded at 90, 80, 70, 60, 50, 55, 65, 75, 85, and 95% saturation, in sequence. A rest period of 2 to 3 minutes was allowed between the tests. Determinations below 65% saturation were attempted only in the normal volunteers. At least 20 points were determined to obtain the curve for each subject at each sitting. The circulation time at the 95% saturation level was determined by extrapolation of the curve.

2. Arm-to-Ear Circulation Time. Following the conclusion of the left heart circulation time determinations, 2 cc. of a 1% solution of methylene blue were injected rapidly through a No. 18 needle into the largest vein in the right antecubital fossa. The stop watch was started at the moment of injection and stopped at the instant of the initial downward swing of the galvanometer beam, which signals the arrival of methylene blue at the ear. The pulse rate was determined during the next 20 seconds. Two to 3 minutes elapsed between each observation to permit the galvanometer to return to normal and to become reestablished by dilution and the consequent decrease in concentration of methylene blue. The needle was kept in the vein until 3 to 5 determinations were done on each subject. On 6 occasions only 2 tests per patient were run. Normal respirations were permitted during the procedure[7]. All determinations were made with the subjects in the supine position under resting, but not basal, conditions. The cubital area of the arm was kept at the auricular level except on a few occasions when the arm was raised above the auricular level to avoid dilution and delay by the slow blood flow in the vein[5]. This maneuver resulted in no significant divergence from the repeated determinations of circulation time made without raising the arm.

Tests with 0.5, 1.0, and 1.5 cc. of methylene blue solution showed that the circulation time did not check satisfactorily with that obtained with the injection of 2 cc. or more of the dye, and the end-point was not as sharp. Determinations with greater amounts of methylene blue did not differ from those with the 2 cc. injections.

Results. 1. Lung-to-Ear Circulation Time. Average lung-to-ear circulation time determined on 23 normal subjects (Table 1) ranged from 4.8 to 7.1 seconds at 95% saturation (Fig. 1). The 12 patients with the various diseases listed (Table 2) showed average left heart times from 4.7 to 10.3 seconds. Variability of individual measures of the circulation time was obtained by calculating the standard deviation of the time from the difference between each circulation time and the average of the series in which that time was obtained. This method of calculating the standard deviation ignores the possibility that variability is a function of the circulation time itself, but this would require a very minor correction to the obtained standard deviation. For the normal subjects the obtained standard deviation by this method was 0.29 seconds and for the patients with chronic disease 0.38 seconds.

The lung-to-ear circulation time shifted in relation to the red blood cell and hemoglobin level. When patients

TABLE 1.—LUNG-TO-EAR CIRCULATION TIME AT 95% SATURATION IN 23 NORMAL SUBJECTS

Subject	*Age*	*Sex*	*Red Blood Count*	*Hemoglobin*	*Circulation Time*	
					Seconds	*Average*
J. R.	27	F	—	14.1	6.0	
M. B.	49	F	—	13.1	5.9	
E. R.	24	M	5.01	15.3	6.0	
M. S.	36	M	4.60	13.4	6.4	
D. B.	26	M	5.23	17.4	5.3	
J. N.	27	M	4.73	15.5	6.0 5.9 5.8	6.0
P. M.	26	F	—	13.4	5.8 6.2 6.0 5.2 5.5 6.5 6.3 5.5 5.7	5.8
H. K.	27	M	4.97	17.6	4.9	
H. B.	33	M	5.6	17.0	6.1 6.3 5.9	6.1
W. E.	24	M	4.66	14.2	5.2	
R. J.	24	M	—	17.5	7.1 6.9	7.0
J. F.	22	M	4.70	13.9	5.7	
J. P.	27	M	—	15.0	7.1 6.9	7.0
M. S.	26	M	—	14.4	6.6 6.9 6.4	6.6
L. J.	24	F	3.94	11.9	5.4	
H. C.	30	M	3.84	12.5	6.1	
E. G.	24	F	4.42	13.3	5.9	
G. W.	26	M	4.55	13.1	6.9	
J. E.	22	M	4.91	14.8	5.3	
H. M.	22	M	4.97	15.6	4.8	
L. D.	28	M	4.60	14.6	6.2	
S. M.	21	M	4.79	14.3	5.3	
J. N.	22	M	5.03	15.3	6.3	

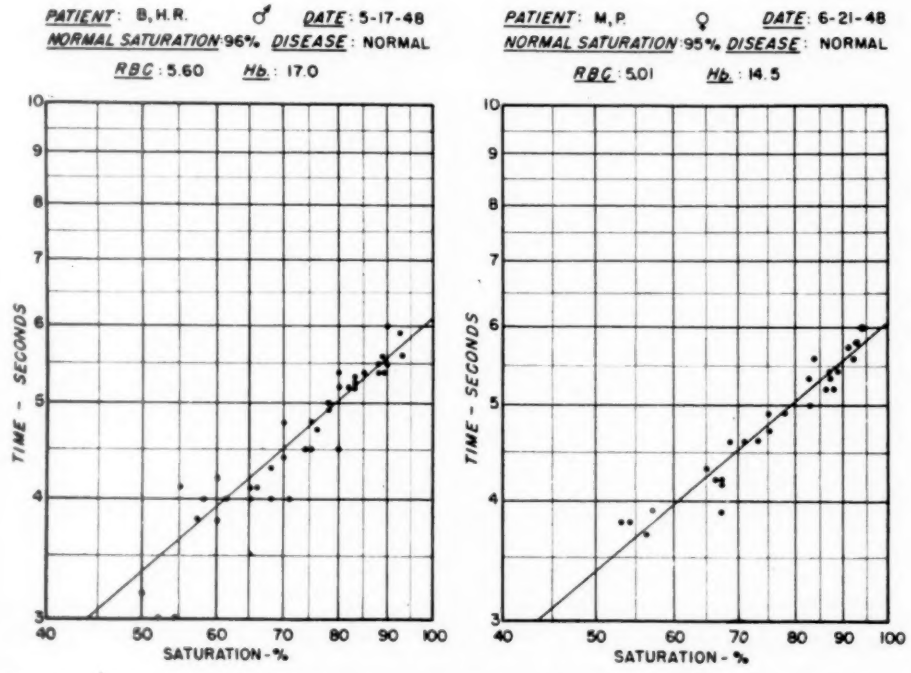
PATIENT: B, H.R. ♂ DATE: 5-17-48
NORMAL SATURATION: 96% DISEASE: NORMAL
RBC: 5.60 Hb.: 17.0
PATIENT: M, P. ♀ DATE: 6-21-48
NORMAL SATURATION: 95% DISEASE: NORMAL
RBC: 5.01 Hb.: 14.5
TIME - SECONDS
SATURATION - %

FIG. 1.—Relationship of arterial oxygen saturation and lung-to-ear circulation time (normal subjects).

TABLE 2.—LUNG-TO-EAR CIRCULATION TIME AT 95% SATURATION IN 12 PATIENTS WITH CHRONIC DISEASES

Subject	*Age*	*Sex*	*Hemoglobin*	*Red Blood Count*	*Circulation Time*		*Disease*
					Seconds	*Average*	
G. B.	26	M	15.9	4.26	6.0		Hodgkin's disease
					6.4	6.3	
					6.5		
A. W.	37	M	13.3	4.04	5.9		Hodgkin's disease
					6.2		
					6.1	6.1	
					5.8		
E. P.	27	M	15.4	5.86	6.0		Extensive bilateral
					6.1	6.1	venous collaterals
					6.1		
E. A.	26	F	15.2	4.25	6.4		Hodgkin's disease
					6.7	6.3	
					6.0		
			14.0	3.82	5.2		
					5.6		
					5.6	5.4	
					5.3		
I. A.	50	M	15.4	5.02	8.6		Mycosis fungoides
					8.3	8.1	
					7.3		

TABLE 2.—(*Continued*)

Subject	*Age*	*Sex*	*Hemoglobin*	*Red Blood Count*	*Circulation Time*		*Disease*
					Seconds	*Average*	
S. G.	53	M	15.1	4.96	7.1		Multiple myeloma
					6.2		
					6.1	6.1	
					5.0		
					6.1		
F. G.	45	F	12.0	3.52	5.2		Multiple myeloma
					4.8		
					4.9	5.0	
					4.7		
					5.1		
T. L.	35	M	14.7	4.42	6.6		Lymphatic leukemia
					6.5		
					6.6		
					6.9		
					6.5		
					6.7		
					6.8	6.8	
					6.9		
					7.3		
					6.8		
					6.7		
					6.8		
R. G.	34	M	15.0	5.08	6.4		Pulmonary sarcoidosis
					6.5		
					6.8		
					7.8		
					7.5	7.0	
					7.1		
					7.3		
					6.8		
					6.4		
W. G.	33	M	13.2	4.29	6.0		Embryoma testes metastatic
					5.2		
					5.4	5.4	
					5.2		
F. B.	58	M	15.4	4.60	7.4		Bronchogenic carcinoma
					7.3	7.3	
					7.1		
W. D.	65	M	18.0	5.31	10.3		Pulmonary emphysema Cor pulmonale

were transfused, both the red cell and hemoglobin levels being raised, the circulation time at 95% increased; as the anemia recurred, the circulation time again became shorter (Fig. 2A). The slope of the curve, however, remained relatively constant despite the rather marked change in the intercept. One patient (D.W.) with cor pulmonale, pulmonary emphysema, and coronary heart disease showed the most prolonged circulation times (Fig. 2B).

Normal subjects were able to tolerate 60% oxygen saturation well, under these circumstances, with the usual symptoms of acute hypoxia. However, it was noted that patients with an anemia were unable to cooperate below 70% saturation. In these patients, as the oxygen saturation fell below 70% apne-

involuntary twitching and lack of response to the verge of unconsciousness occurred.

2. Arm-to-Ear Circulation Time. Determinations of arm-to-ear circulation rate made on 32 normal subjects yielded a range of average time from 9.6 to 19.9 seconds (Table 3). Corresponding rates were determined for 17 hospital patients with various dis-

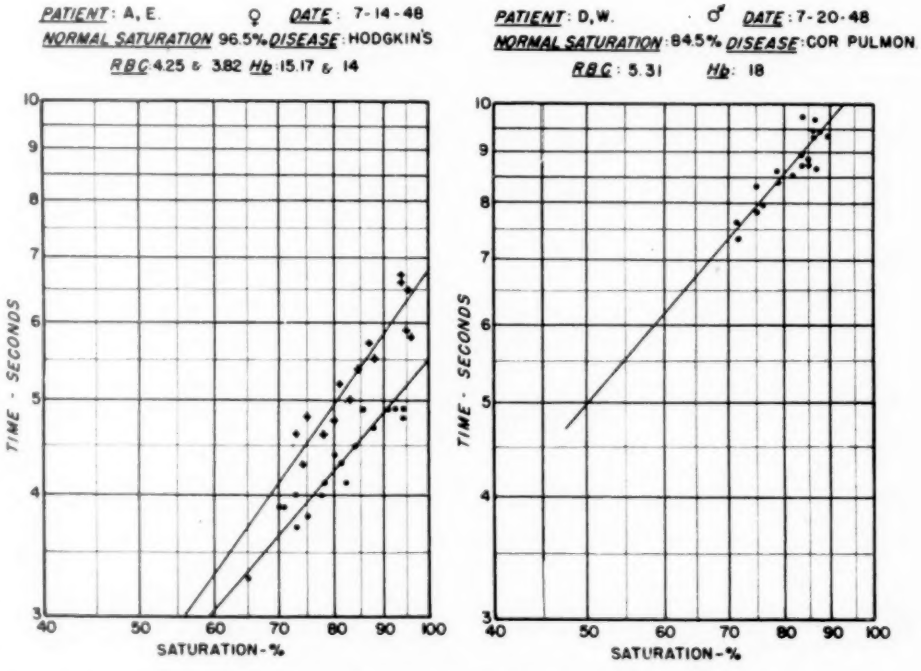

Fig. 2.—Relationship of arterial oxygen saturation and lung-to-ear circulation time.

2A, left. AE. female, July 14, 1948: Shift of the curve with blood transfusion. Previous curve determined when RBC was 3.82 million and Hb was 14.0 gm. After transfusion RBC was 4.25 million and Hb was 15.17 gm.

2B, right. DW. male, July 20, 1948: Marked increase in lung-to-ear circulation time in patient with cor pulmonale, coronary heart disease, and pulmonary emphysema.

TABLE 3.—ARM-TO-EAR CIRCULATION TIME IN 32 NORMAL SUBJECTS

Subject	*Age*	*Sex*	*Red Blood Count*	*Hemoglobin*	*Circulation Time*	
					Seconds	*Average*
E. D. N.	30	M	5M	14.5	14.2	
					12.9	13.5
					13.3	
A. M.	23	M	PCV = 45	15.1	12.2	
					13.9	
					11.7	12.2
					11.0	

TABLE 3.—(*Continued*)

Subject	*Age*	*Sex*	*Red Blood Count*	*Hemoglobin*	*Circulation Time*	
					Seconds	*Average*
R. I. H.	27	M	5.5M	16.0	14.0 12.3 13.8 13.2	13.4
P. H. T.	22	M	—	—	12.0 10.6	11.3
H. G. P.	21	M	PCV = 48	16.9	11.5 12.3 12.8	12.2
M. P.	27	M	5.5M	17.0	10.9 10.3	10.6
H. Y. L.	26	M	5.2M	16.0	15.4 13.4 13.2	14.0
M. P. T.	28	M	5.1M	15.2	11.6 12.1 12.5	12.1
M. L. W.	21	M	5.0M	14.5	8.5 10.9 11.0	10.1
V. E.	36	M	—	—	10.0 11.2 11.4 12.3	11.2
J. P.	29	F	4.5M	14.7	14.1 13.9 13.2 14.1 13.9	13.8
S. R. M.	21	M	4.5M	14.0	13.8 14.4	14.1
P. G. M.	21	M	5.4M	15.5	12.7 14.2 11.0	12.6
R. P. P.	30	M	5.0M	14.7	9.8 9.6 9.7 9.4	9.6
H. R. B.	33	M	5.6M	17.0	12.8 12.7 11.5 12.2	12.3
C. B. S.	22	M	4.9M	15.0	15.2 15.0 16.0 15.3 16.0	15.5
T. G. S.	26	M	5.0M	16.0	14.0 15.0 15.1 14.7	14.7

TABLE 3.—(*Continued*)

Subject	*Age*	*Sex*	*Red Blood Count*	*Hemoglobin*	*Circulation Time*	
					Seconds	*Average*
A. D. S.	25	M	5.0M	15.0	11.0	
					12.2	
					12.0	11.8
					12.0	
K. F. S.	34	M	4.8M	13.0	9.3	
					10.8	
					10.1	10.2
					10.6	
H. C.	30	M	3.8M	12.5	13.2	
					13.3	13.2
					13.2	
L. J.	24	F	3.9M	11.9*	9.7	
					9.1	
					8.8	9.9
					10.2	
					10.5	
E. G.	24	F	4.4M	13.3	19.3	
					17.9	
					12.3	15.5
					12.5	
J. N.	22	M	5.0M	15.3	19.9	
					16.8	
					20.8	18.6
					16.0	
W. E.	24	M	4.7M	14.2	12.8	
					15.9	
					14.8	14.6
					15.3	
H. K.	27	M	5.0M	17.6	11.9	
					11.7	
					11.1	11.8
					12.4	
D. B.	26	M	5.2M	17.4	20.9	
					18.3	18.8
					17.2	
L. D.	28	M	4.6M	14.6	12.4	
					11.6	
					11.2	11.8
					12.6	
					11.3	
P. M.	26	F	—	13.4	11.4	
					10.4	10.9
S. M.	21	M	4.8M	14.3	15.4	
					14.7	
					15.2	14.7
					13.3	
J. E.	22	M	4.9M	14.8	15.1	
					12.4	
					12.8	13.4
					13.2	
H. M.	22	M	5.0M	15.6	13.5	
					14.3	14.0
					14.1	
J. F.	22	M	4.7M	13.9	19.9	
					20.0	19.9
					19.8	

* Second day of menses.

TABLE 4.—ARM-TO-EAR CIRCULATION TIME IN 17 PATIENTS WITH CHRONIC DISEASES

Subject	Age	Sex	Disease	Hemoglobin	Red Blood Count	Circulation Time	
						Seconds	Average
E. N.	27	M	Hodgkin's disease	13.9	3.94	11.2	
						11.1	11.2
E. A.	26	F	Hodgkin's disease	11.8	3.58	12.3	
						14.3	12.8
						11.8	
S. G.	52	M	Multiple myeloma	15.1	4.96	10.6	
						11.8	
						11.7	
						11.2	
						11.2	
						11.2	
						11.4	
						11.8	11.5
						11.3	
						11.5	
						11.2	
						11.6	
						11.6	
						11.7	
						11.8	
						11.8	
R. G.	33	M	Pulmonary sarcoidosis	15.0	5.08	13.2	
						14.2	
						12.2	
						14.6	
						12.5	
						14.0	
						12.0	
						12.4	
						14.1	
						12.5	12.7
						13.2	
						15.0	
						13.0	
						11.6	
						10.2	
						10.7	
						10.8	
						10.6	
						12.2	
						14.1	
G. B.	26	M	Hodgkin's disease	15.9	5.59	11.6	
						10.6	11.1
T. L.	31	M	Lymphatic leukemia	14.7	4.42	14.6	
						14.4	
						11.5	
						14.5	13.1
						11.4	
						13.7	
						11.6	
F. C.	55	M	Carcinoma bronchus	—	—	10.4	
						10.9	10.6
F. G.	48	M	Carcinoma bronchus	14.1	3.99	8.2	
						7.3	7.8

TABLE 4.—(*Continued*)

Subject	*Age*	*Sex*	*Disease*	*Hemoglobin*	*Red Blood Count*	*Circulation Time*	
						Seconds	*Average*
L. B.	55	M	Hypertensive CVD marked dyspnea	—	—	19.8 22.4 22.8	21.7
F. A.	50	M	Mycosis fungoides	15.4	5.02	18.5 16.7 16.8	17.3
F. F.	58	M	Mycosis fungoides	16.5	4.34	15.4 17.6 15.1	16.0
R. B.	65	F	Carcinoma breast	13.7	3.00	12.6 11.3 11.5	11.8
V. Z.	66	M	Angina pectoris, asthma	—	—	22.7	22.7
C. L.	63	M	Morphine addict	—	—	11.0 13.5	12.3
A. W.	37	M	Hodgkin's disease	13.3	4.04	9.4 9.3 8.8 9.0	9.1
F. B.	58	M	Bronchogenic carcinoma	15.4	4.60	10.8	10.8
W. G.	32	M	Carcinoma testis	13.2	4.29	9.4 8.7 10.4	9.5

eases(Table 4). The average circulation time ranged from 7.8 to 22.7 seconds. Variabilities computed in the same manner as for lung-to-ear times gave a standard deviation for normal subjects of 0.68 seconds and for the patients 0.79 seconds.

In the course of the study it was determined that the intravenous injection of as much as 10 cc. of 1% methylene blue in 2 cc. increments was nontoxic, although in some individuals a dull ache was experienced for a few seconds along the course of the basilic or cephalic vein when injections of this amount were given. This disappeared in most instances within a few minutes, although in 1 individual some discomfort was noticed for 1 day following the test. A few patients have complained of lightheadedness and abdominal discomfort after the 2nd or 3rd injection, at which time the oxygen saturation has been noted to fall below 90%. Inhalation of 100% oxygen for 2 to 3 minutes caused the oxygen saturation to rise to 95% associated with the prompt disappearance of complaints, so that further trials were continued. However, the majority of patients had no untoward reaction from the procedure. No appreciable change in pulse rate during the circulation of the dye was noted.

Discussion. The relative nontoxicity of methylene blue permits repeated observations at frequent intervals with multiple checks during a single venous puncture over the course of 10 minutes.

Since it has been shown that the uptake of oxygen by hemoglobin occurs almost instantaneously[6], the major delay in the left heart circulation time

determination is most probably one of diffusion of oxygen from the mouth to and through the alveoli. Lung-to-ear circulation times at 95% saturation usually average over 6.5 seconds. This is shorter than the lung-to-ear times reported with the oxygen inhalation method[4]. It would appear that the shorter lung-to-ear circulation times obtained by the nitrogen inhalation method[20] might be misinterpreted since the circulation time may have been measured at a saturation less than 95% without correction for the delay in nitrogen diffusion or partial anoxia. For determining the lung-to-ear circulation time at or above 95% saturation, the data presented would agree with the opinion of Fowler and Comroe[4] that inhalation of oxygen is a more reliable method. However, the slow, minimal movements of the galvanometer at this saturation make it difficult to check repeated determinations.

The demonstration of a direct relationship between left heart circulation time and hypoxia may further alter the interpretation of circulation times in patients with cardiac or pulmonary disease associated with decreased arterial oxygen saturation. In the latter case, long circulation times would be even more prolonged if extrapolated to 95% saturation for true comparison with the normal values.

The curves of lung-to-ear time were obtained on at least 20 determinations at saturations from 65 to 92%. The straightest line possible was drawn through these points. In some instances it appeared that a flattening toward the horizontal at 85 to 100% saturation fitted the points best, the curve being similar to the oxyhemoglobin dissociation curve. This is quite difficult to determine in most cases, however, since the changes in galvanometer deflection are minimal at 95 to 100% saturation.

A possible explanation of the shortened circulation time with increasing hypoxia may be either vasoconstriction of the pulmonary vascular tree or increased output by the left ventricle, both of which are reported to occur[9, 14, 19]. The significance of the curve and of its shape is presently being evaluated.

The small number of patients does not permit any valid comparison with normals other than to note that there was more variability in the determinations than was encountered with the normal subjects.

The technique described affords a simple, accurate method for determining the circulation time of the venous and arterial components of the arm-to-ear circulation route. The employment of these methods during intra-cardiac and intra-arterial catheterizations may be of value in further defining the disturbances of transport time in specific segments of the circulation.

Summary. 1. An objective method, utilizing the oximeter, for determining arm-to-ear and lung-to-ear circulation times is described.

2. The arm-to-ear circulation time by this method in 32 normal subjects was 9.6 to 19.9 seconds; for 17 patients with chronic illnesses the time was 7.8 to 22.7 seconds.

3. The lung-to-ear circulation time at 95% saturation in 23 normal subjects was found to be from 4.8 to 7.1 seconds; on 12 patients with chronic diseases with alterations of the red blood cells and hemoglobin, it ranged from 4.7 to 10.3 seconds.

4. A direct relationship between the left heart circulation time and arterial oxygen saturation at hypoxic levels has been demonstrated. The curve obtained changed in response to increasing or decreasing anemia.

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TYPHOID FEVER OF SHORT DURATION

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It has been known for a long time that typhoid fever may run a short, mild course, particularly in children[1]. Virchow is quoted as saying he had never seen children die of the disease and is reported to have taught that typhoid fever very rarely occurred in children. Yet in well controlled epidemiologic studies[3] it has been found that in epidemics, as well as in endemic areas, children came down with the disease first and most frequently. This fact appears to have been neglected in the literature of recent years and frequently has led to delayed diagnosis.

The present study attempts to determine the incidence of such mild cases.

Material. All case records of patients with typhoid fever admitted to the Communicable Disease Unit of the Los Angeles County Hospital between July, 1938, and July, 1948, were reviewed. A total of 346 definitely proved cases was found. Carriers were excluded.

Of these patients, 47 (11.3%) had an atypical course which had led to greatly delayed diagnosis. (Table 1). These were grouped together because they met the following criteria:

Bacteriologic or serologic proof of typhoid fever, a minimum of clinical symptoms, a short course of the disease with little rise in temperature, and a normal or elevated white blood cell count.

Clinical Data. *Diagnosis.* Positive blood cultures or positive stool cultures and high titers or rising titers of agglutination were found in all patients. The agglutination titer was in no way different from that of patients with "typical" typhoid fever.

Previous History of Typhoid Fever. This was not obtained in a single patient.

Immunizations. Not a single patient had been immunized against typhoid fever or paratyphoid fever.

Age Incidence. This is shown in Table 2.

Race. Of the 47 patients, 40 were Caucasian, 4 were Negroes, and 3 were orientals.

Predominant Symptoms. Cough, nonproductive and hacking, and upper respiratory symptoms predominated. Constipation and diarrhea were second. Almost all of the patients were noted to have both cough and either constipation with abdominal discomfort or watery diarrhea at the same time.

Epistaxis was present in 2 of the 47 patients within the first week of the disease.

Stupor was commented on in all of the patients. The descriptions given b

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the admitting residents were "quiet", "listless", "somnolent", and so forth, and some of the residents found this most unusual, particularly in the smaller children.

Temperature. The temperature curves of all the patients had one thing in common: the short duration of fever. The average duration was 10 days. Otherwise the temperature was very different in different patients. There was no characteristic pattern. In some there was rapid rise within 2 or 3 days up to 103° F. and plateau-type fever with rapid defervescence, in others the morning temperatures were normal, with afternoon fever not exceeding 101° F. There was no correlation between the degree of fever and severity of symptoms.

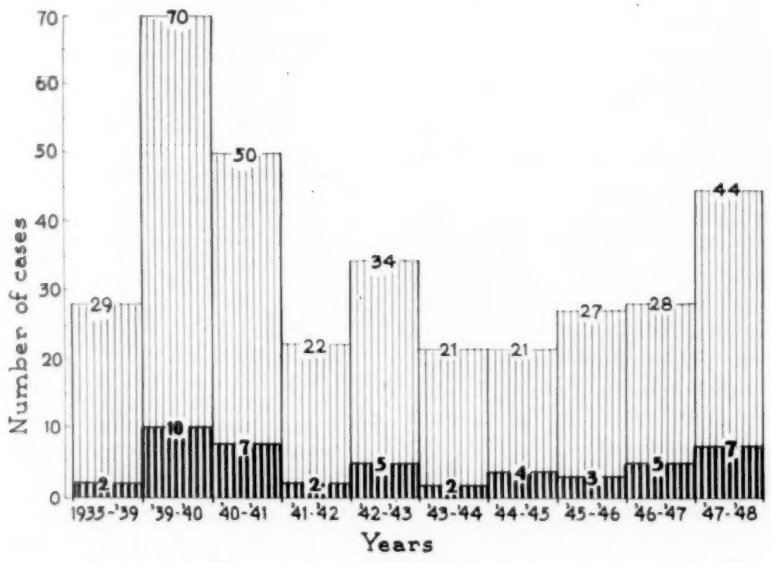

FIG. 1.—Total (346) and mild (47) cases of typhoid fever admitted to Los Angeles County Hospital, 1935 to 1948 (indicated by shaded areas).

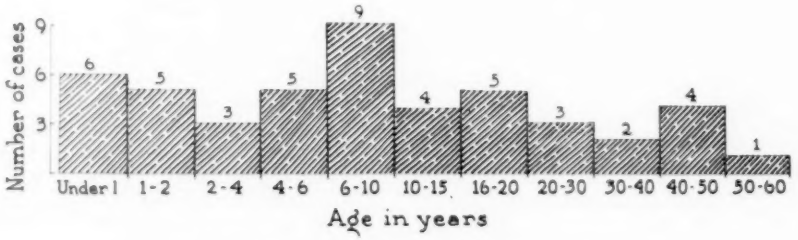

FIG. 2.—Age distribution of mild cases (47).

Pulse. There was nothing characteristic about the pulse rate noted on the charts of these patients.

Blood Picture. In most of the patients the white blood cell count was within normal limits; in one patient without complications there was initial leuko-

cytosis up to 20,000 white blood cells. The differential count consistently revealed predominance of mononuclear cells, mostly around 50 to 60%, even in the patients over 6 years of age. Other than that, there were no significant findings.

Rose Spots are noted in the charts of only 2 patients. It is inconceivable that they were not present at some time or other in greater or lesser degree in the majority of these cases. Unquestionably these tiny spots were observed and dismissed as not significant by those uninitiated in typhoid.

Complications. No patient had complications. All recovered promptly. Three patients were thought to have otitis media on admission and one had a subcutaneous abscess of the thigh on admission, presumably due to hypodermic medication.

Carrier State. One of the patients became a stool carrier.

Diagnoses Made on Admission. None of the patients was originally referred to the Communicable Disease Unit. The diagnoses of referring physicians and admitting resident physicians were "bronchopneumonia," "gastroenteritis," "nasopharyngitis," "fever of undetermined origin," and others. In a few of the patients typhoid fever or some other bacteremia was suspected and blood cultures and agglutinations drawn on admission, but a lapse of at least 2 days occurred in each case before the diagnosis was established.

Films of the chest and sinuses were taken in all cases where the admitting diagnosis indicated involvement of the chest or sinuses. They were reported as negative in each instance.

Some illustrative cases are presented.

Case Reports. CASE 1. D. K., LACH. No. 819950, a 3-month-old Caucasian male child, was admitted with a history of fever of 101° F., restlessness, belching and flatus, and watery diarrhea of 5 days' duration. The child had been delivered by cesarean section at 8½ months, birth weight 5 lb., 3 oz. It had been well until 2 months of age when it was in the hospital for severe infectious diarrhea due to *Shigella* Flexner. The patient recovered promptly after nonspecific therapy had been given, including 2 blood transfusions. One week before admission the mother noted marked salivation and bleeding from the tongue; the baby had difficulty holding the nipple so that a dropper had to be used. Two days later, fever was first noted (100° F. to 101° F. every night). The next day greenish diarrhea appeared. The stools contained much mucus, never any blood. The child had not been immunized.

On admission to the hospital the baby was listless. Weight was 9 lb., 8 oz. Temperature was 103.8° F., pulse 160, respirations 36. The skin was dry and hot. The tongue was red, but no bleeding points were found. The chest was clear and the abdomen was markedly distended. No organs or masses could be palpated.

Urine analysis was entirely normal. Blood data included hemoglobin 8 gm., red blood cells 2.9 million per c.mm., white blood cells 9900 with 58% mononuclear cells and 42% polymorphonuclear cells. Agglutination tests were negative but a blood culture taken on admission and 2 subsequent blood cultures were positive for *S. typhosa.*

CASE 2. R. H., LACH. No. 751358, a 2½ year old Caucasian male child, was first seen by his family physician because of sore throat, pain in the legs and arms, and listlessness. Three days later the patient had a shaking chill and a temperature of 103° F. From that time on the temperature was about 100° F. every morning and 104° F. every afternoon. Nonproductive cough developed on the 5th day of illness. The pulse rate was around 100 per minute. Sulfapyridine was administered by the private physician without effect and the patient was admitted to the Los Angeles County hospital where he was found to be very listless, but no abnormal findings were noted on the chart. Hemoglobin was 13 gm., red blood cells 5 million per c.mm., white blood cells 20,000 with 70% polymorphonuclears, 22% lymphocytes, and 8% monocytes. A blood culture grew *S. typhosa.* On the 9th day of illness careful search revealed rose spots on the abdomen and on the chest, after which he was afebrile.

CASE 3. R. A., LACH. No.727280, a 6-year-old Caucasian boy, attended a picnic on June 30, 1940. On July 15, 1940, he com-

plained of vague aches and pains in his legs and his back. His temperature was found to be 101° F. He continued to be up and around and on the 3rd day of his illness he had a bout of diarrhea accompanied with mild epigastric pain. Still he continued to be up and to play with his friends. In the second week of the illness he lost his appetite and became constipated. A physician found a temperature of 101°F. and sent the boy to the hospital. The patient had never been immunized against typhoid fever.

Examination at the hospital revealed a well developed, well nourished boy lying quietly in bed without complaints. Temperature was 100° F., pulse 88 per minute. There were increased breath sounds noted over both hilar areas posteriorly, the abdomen was slightly distended, and there were no rose spots. The hemoglobin was 13 gm., the white blood cells numbered 8500 per c.mm., with 50% polymorphonuclears and 50% mononuclears. Urine analysis was normal. Serum agglutination tests revealed agglutination for S. *typhosa* in dilution up to 1:1280. Blood cultures, stool cultures, and urine cultures were negative. The patient was entirely asymptomatic and his temperature became normal within 3 days.

A roentgenogram of his chest was normal on admission.

Comment. The present study bears out the experience of older clinicians that in epidemics of typhoid fever school children frequently complain of vague abdominal symptoms without ever missing school. That this also happens in endemic areas is demonstrated in this analysis. If careful histories are taken, most of the characteristic symptoms of typhoid fever are found to be present, particularly diarrhea, constipation, abdominal discomfort and distention, chills, cough, and headaches. Prompt laboratory proof should then be sought.

Of Stuart and Pullen's[2] 360 cases of typhoid fever, slightly more than 1/3 occurred in children. However, these writers make no mention of the fact that the disease may run a short and mild course in the young.

The present authors found that one of the main reasons for delayed diagnosis was the normal or elevated white blood cell count. Dowling[1] states that the leukocyte count is rarely above 10,000 per c.mm., unless complications such as hemorrhage, perforation, pneumonia, phlebitis, cholecystitis, or unrelated infections, such as furuncles or abscesses, are present. While generally true of adults, this was not borne out in our patients. Only 1 patient had an abscess on admission and all patients recovered promptly. Stuart and Pullen found white cell counts ranging from 1200 to 20,000 cells in apparently uncomplicated cases. They also usually found a transient rise in the white blood cell count during the first 10 days of the disease in their review of 360 patients.

The listlessness and somnolence observed in the authors' patients was a very constant symptom and should point to the correct diagnosis.

Summary and Conclusions. 1. Of all cases with proved typhoid fever admitted to the Communicable Disease Unit of the Los Angeles County Hospital between 1938 and 1948, 11.3% were found to run a short course of their disease characterized by mild symptoms, little rise in temperature, and a normal or elevated white blood cell count.

2. These cases of short duration averaged 10 days of fever and were predominately in children or young adults.

3. None of these patients had been immunized against typhoid fever.

4. All of the patients recovered and there were no complications.

5. The paucity of symptoms and the

absence of leukopenia were mainly responsible for the delay in diagnosis.

6. Listlessness and somnolence were present in all of these cases.

7. Typhoid fever in the young may run an atypically mild course. The epidemiologic implication of these findings is self-evident.

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NPH INSULIN IN DIABETIC PATIENTS WITH COMPLICATIONS

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In diabetic patients having complications of surgical or medical nature, the use of protamine-zinc insulin alone is generally unsatisfactory for maintenance of adequate metabolic control. The rate of absorption of insulin from subcutaneous depots of standard protamine insulin preparations is too slow to respond to the physiologic needs of the situation. Likewise, in the unstable diabetic patient, protamine insulin does not handle the postprandial metabolic load. Mixtures of regular insulin and protamine-zinc insulin have been widely employed in recent years because of these deficiencies[2,3,16,17]. The authors' experience with insulin mixtures in the complicated diabetic patient has been favorable.

Insulin requirements are increased by fever, surgery, trauma, and other concomitant disease states. Increased requirements under these circumstances may be the result of: a) activation of the adrenal cortex with release of steroid hormones which reduce glucose tolerance and antagonize the action of insulin; b) elevation of temperature which increases rate of cellular metabolism; c) increased destruction of insulin by proteolytic enzymes; d) decreased hepatic cellular function in glycogen formation and release. Any one or several of these mechanisms may operate in the presence of infection, gangrene, or surgery. The purpose of this paper is to evaluate the use of NPH insulin* in the presence of these complications.

The development of a new modified protamine insulin (NPH) during recent years has emerged from the efforts of McBryde and Roberts[10], Peck[13,14], and Colwell[1]. A suspension of crystals of protamine-zinc insulin was prepared by Krayenbühl and Rosenberg[9], from which is produced a solution containing no uncombined protamine, practically all insulin activity being in the crystalline precipitate. The physical characteristics of this preparation are discussed by Colwell[2], Peck[14], and Izzo[6]. The time-action blood glucose curves obtained with NPH insulin (Neutral Protamine Hagedorn) closely resemble those of 2:1 mixtures of regular and protamine insulin as determined by Colwell[2], Dolger[4], and Izzo[6]. Problems in the manufacture of a stable form of these protamine-zinc insulin crystals in neutral suspension have been solved.

Reports concerning the use of NPH insulin in several groups of patients have appeared[4,5,7,8,11,18]. For the most part these have dealt with the treatment of uncomplicated diabetics, young diabetics[5,18], or pregnant diabetics[18].

The present study was conducted in hospitalized patients all of whom, with one exception, were admitted for

* Supplied by E. R. Squibb and Sons.

treatment of a complication of diabetes. NPH insulin was given to each patient during the period when the complication was an important factor in the management. Diabetic coma was treated with regular insulin until the patient had responded to therapy, at which time NPH insulin was given and supplemented with regular insulin if needed. This conversion to a depot, intermediately-acting form of insulin was usually accomplished within 72 hours.

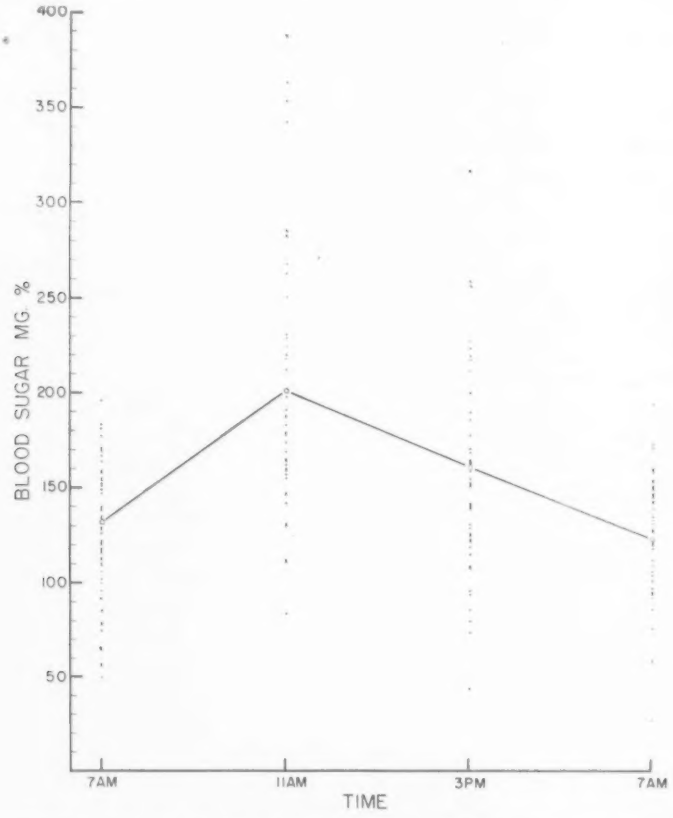

FIG. 1.—Composite curve of 64 blood sugar curves obtained with 33 patients following a single pre-breakfast dose of NPH insulin.

Methods and Materials. The 33 patients used in this study included both initially and previously diagnosed diabetics admitted to the medical or surgical wards for treatment of various complications. The onset of symptomatic diabetes was provoked by the complications in 8 cases; the remainder of the patients had received insulin therapy for intervals of 6 months to 12 years. It was considered unnecessary to classify these patients as to stability of their diabetic state. In the presence of the complicating processes listed in Table 1, metabolic aberrations fluctuate more widely, and the response to insulin is more unpredictable, than in uncomplicated diabetes. Thus these patients were relatively unstable in their response to diabetic management.

In each patient the dose of NPH insulin necessary to control the fasting blood glucose was determined. This was accomplished either by giving regular insulin as indicated

TABLE 1.—REPRESENTATIVE BLOOD SUGAR CURVES ON 33 DIABETIC PATIENTS RECEIVING NPH INSULIN

Patient	Age	Average Daily Dose	Mean Venous Blood Sugar				Complications
			8 A.M.	11 A.M.	3 P.M.	8 A.M.	
1	69	90	102	211	128	86	Hyperthyroidism, pneumonia, diabetic coma
2	36	90	126	188	164	131	Acute pyelonephritis, diabetic coma
3	33	80	70	149	108	77	Abscess and cellulitis dorsum left hand (incision and drainage)
4	22	72	50	147	44	59	Vulvovaginitis, diabetic coma
5	72	64	155	220	119	158	Adenocarcinoma of breast, radical mastectomy
6	34	56	159	244	147	129	Excision condyloma accuminata
7	64	48	109	188	153	76	Phimosis (dorsal slit), cellulitis, avitaminosis
8	60	48	114	162	126	117	None. Initial diabetes
9	52	48	140	212	204	139	Gangrene, cellulitis, osteomyelitis left foot (amputation of leg)
10	46	48	161	211	231	144	Transverse myelitis, paraplegia, cord bladder, cystitis
11	69	44	129	218	228	109	Right great toe abscess and cellulitis
12	78	42	137	196	130	130	Calf thrombophlebitis, removal pessary (Leforte colpocleisis)
13	82	40	169	188	178	173	Excision squamous cell carcinoma of hand
14	57	40	120	191	109	159	Severe diabetic neuropathy
15	55	40	167	264	230	147	Gangrene right 1st toe, diabetic coma
16	54	40	100	112	80	86	Acute otitis media, chronic mastoiditis
17	40	40	181	231	200	173	Hypertensive cardiovascular disease, myocardial insufficiency
18	71	30	141	182	135	149	Gangrene left leg, skin graft
19	68	30	127	230	168	166	Gangrene and osteomyelitis left foot (amputation 2nd toe and metatarsal head)
20	58	30	135	179	125	121	Varicose ulcer left leg (vein ligation)
21	40	30	180	365	288	119	Rheumatic heart disease, myocardial insufficiency
22	66	28	109	84	151	124	Chronic cholecystitis, hypertensive cardiovascular disease
23	64	26	85	213	142	108	Gangrene left 2nd toe (saphenous ligation)
24	62	24	164	354	224	158	Severe anxiety reaction
25	55	22	122	157	198	129	Acute cholecystitis (cholecystectomy), leiomyoma of stomach (gastrotomy)
26	73	20	169	178	169	142	Carcinoma of pancreas, metastasis to liver, pulmonary infarction
27	68	20	114	171	166	120	Hypertensive heart disease with myocardial insufficiency, cataract extraction
28	65	20	115	154	158	124	Intertrochanteric fracture left femur (open reduction), carcinoma of cervix with spread to rectum, rectal stricture and bleeding
29	50	20	137	247	176	143	Gangrenous ulcer of left heel
30	73	16	161	185	222	151	Cerebral thrombosis, hypertensive heart disease with myocardial insufficiency
31	66	16	110	160	123	95	Gangrene of left foot (amputation left leg)
32	51	16	164	159	169	153	Dilatation and curettage, cervical biopsy
33	76	14	124	203	149	102	Choledocholithiasis, chronic cholecystitis, diverticulitis of sigmoid colon

for 24 to 72 hours to determine the approximate 24-hour requirement of insulin, or by supplementing an estimated dose of NPH insulin with regular insulin as demanded by positive urine sugar determinations. When a single dose of NPH insulin seemed adequate, a series of venous blood glucose determinations was obtained at 7:00 A.M., 11:00 A.M., 3:00 P.M., and 7:00 A.M. the following day (blood glucose curve). Subsequent diurnal fluctuations were studied when the diet or the clinical course were altered. By such a procedure it was possible to evaluate the effectiveness of NPH insulin in the control of the diabetic patient with complications.

During treatment with NPH insulin, blood glucose curves were obtained 64 times in the 33 patients. Some patients also received mixtures of regular and protamine insulins and globin insulin for comparison with NPH insulin. These results are not discussed in this report. The venous blood glucose determinations were performed by Nelson's photometric adaptation of the Somogyi method[12]. Fractional urine sugar determinations were made daily at 7:00 A.M., 11:00 A.M., 4:00 P.M., and 9:00 P.M.

No blood glucose curves were obtained until the patient was able to consume a weighed diet which was calculated on the basis of the nutritional needs in each instance. In Patient 10, who had transverse myelitis at dorsal vertebra 5 and urinary tract infection, it was necessary to give a total of 3600 calories with 2.5 gm. of protein per kg. of ideal body weight. Obese patients, on the other hand, were maintained on a hypocaloric diet. In the entire group, the protein intake ranged from 1 gm. to 2.5 gm. per kg. of ideal weight; the carbohydrate intake ranged from 120 gm. to 380 gm. Unconsumed carbohydrate on the tray was replaced by orange juice at each meal. Adjustment of the carbohydrate distribution was made whenever indicated. Frequently a shift of 15% of the carbohydrate from breakfast to another time was desirable because of positive urine sugar at 11:00 A.M. This will be discussed in greater detail.

Results. The values listed in Table 1 represent the composite blood glucose curves obtained in each case. The insulin dose recorded is that which was being administered at the time of the test. The patients are arranged according to the amount of insulin received, but the size of the dose is not necessarily an indication of the clinical response of the patient to the treatment. Some of those requiring relatively small amounts of insulin had wide fluctuations in blood sugar, for example, Patients 24 and 29. Such individuals have a high blood sugar without insulin but respond to the administration of small doses. The unstable patient presents the same problems from the standpoint of fluctuation and the need for close observation whether his insulin requirement is large or small. NPH insulin appears to be of value in the control of these patients.

It will be noted that diabetic coma was included among the complications in 4 instances. Each of these patients received initial treatment with regular insulin for several days. Upon recovery from acidosis they were given the NPH preparation while specific treatment was being administered for the complication which precipitated acidosis. Gangrene was responsible for 8 of the admissions; amputation was necessary in 3 of these, each receiving NPH insulin during the period of surgical management. Infectious processes with fever and associated manifestations were present in 12 patients. With the more serious complications it was often necessary to supplement NPH insulin with additional doses of regular insulin during the first few days of treatment. In these cases, blood glucose curves were obtained when the acute process was subsiding. Cholecystitis was present in 3 patients, on 2 of whom cholecystectomy was performed and to whom NPH insulin was given through the period of surgical management. Congestive heart failure was the complication necessitating admission in 4. One of these suffered an episode of cerebral thrombosis and on another a cataract extraction was performed following restoration of compensation.

The response to NPH insulin was satisfactory throughout the hospital course with the exception of Patient 21. In this instance it was necessary to give regular insulin together with the NPH preparation in the same syringe in order to reduce the postprandial blood sugar to more acceptable levels. The initial diabetic patient with no complications (Patient 8) was included as representative of the control found in a relatively stable diabetic given NPH insulin. Her insulin requirement was 90 units per day initially, but this fell rapidly to 48 units within five days of admission and remained at that level until discharge, during which time the 3 blood glucose curves obtained were indicative of entirely adequate diabetic control.

Two methods for effecting better utilization of carbohydrate were employed occasionally. It was noted that an improvement in the blood glucose curves was obtained following a reduction in the breakfast carbohydrate ration to 20% of the daily total. This has been necessary in about half of the patients receiving NPH insulin. The redistributed carbohydrate may be given at supper and bedtime. Additional regular insulin was added to the daily NPH dosage in 5 patients manifesting a high morning postprandial rise in blood sugar. This would be equivalent to a 3 or 4 to 1 regular protamine mixture, depending upon the amount of insulin used. It is interesting to note that, in these patients, the average fasting blood sugar dropped from 151 mg. to 130 mg., and the postbreakfast sugar from 249 mg. to 205 mg. following this addition. Apparently regular insulin retains most of its prompt action when added to the saturated protamine-zinc insulinate suspension.

There have been 5 instances of insulin sensitivity of the common local urticarial type in this small series. In no instance has NPH insulin been discontinued because of this. Throughout the study there occurred but 3 hypoglycemic reactions to NPH insulin and these were characterized by weakness, sweating, faintness, and hunger. Two patients not included in the present study developed severe reactions to NPH insulin; one experienced a convulsion, the other extreme weakness with bigeminy.

There has not been a complete follow-up on most of these patients. Those who have returned to the clinic have been maintained with normal fasting blood sugar and, with several exceptions, adequately controlled fractional urine sugars. However, blood glucose curves have not been obtained. It would be desirable to observe whether the activity of daily life outside the hospital further reduced the postprandial blood glucose, especially during the morning hours. Study of the blood glucose curves published by Gabriele and Marbel[5,11], White[18], and others[2,7,8] in several large series of active and uncomplicated diabetic patients indicates that the effect of NPH insulin on the ambulatory groups is quite similar to that observed in the complicated hospitalized patient.

Discussion. Important factors in the metabolic control of the diabetic patient during surgery or infection are: the avoidance of water and electrolyte losses occasioned by sustained glycosuria; the reduction of nitrogen losses associated with protein glyconeogenesis (by increasing utilization of carbohydrate), and the prevention of fat mobilization and acidosis with disruption of enzymatic activity and disorganization of intracellular biological processes necessary for recovery. These ends may be achieved by insulin therapy and attention to nutritional needs. With respect to insulin, it must

be provided in a form capable of prompt and effective action. The results of the present observations indicate that NPH insulin possesses a rapid phase of activity which is generally adequate for use in diabetic patients with complications of medical or surgical types, and a prolonged action which tends to stabilize blood glucose levels throughout the 24-hour period.

One of the criticisms against the new insulin is its failure to control the post-breakfast blood sugar in some patients[4]. The 2 procedures used to counteract this have been mentioned previously. The simpler and usually effective method is to transfer 10 to 15% of the carbohydrate from breakfast to an interval afternoon or bedtime feeding. Such redistribution is actually desirable in the majority of cases since the peak of action of this insulin occurs in the late afternoon or evening hours and the tendency to mild hypoglycemic reactions at these times is thus obviated. Occasionally it may be necessary to add regular insulin to the syringe containing the NPH insulin to prevent excessive morning glycosuria. This has been required in 5 patients in the present group. It should be understood, furthermore, that NPH insulin does not act with sufficient promptness and intensity to be effective in the treatment of coma and severe acidosis.

One of the advantages of NPH insulin is that it permits early conversion from regular insulin. The benefits of early conversion to a longer-acting preparation are several. In the first place, the estimation of the insulin dose is simplified and the necessity for frequent injections is overcome except for occasional instances wherein supplementation with regular insulin is required. If the fractional urine sugars are positive following an inadequate dose, additional regular insulin is given at the respective meals and at 3:00 A.M., if indicated. Should the fasting blood glucose be low on the day a certain dose of NPH is given, additional carbohydrate in the form of orange juice is administered several times throughout the day unless urine sugars become positive. Secondly, standardization of the patient is achieved earlier in his hospitalization, during most of which period a depot insulin is administered. The initial dose of NPH insulin replaces the multiple doses of regular insulin upon which the 24-hour requirement is based. In changing to the NPH preparation, the largest dose in this study was 160 units given to 2 patients emerging from acidosis, no supplements of regular insulin being required. Progressive decrements of these doses were prescribed until the condition became stabilized and a maintenance dose was ascertained. Thirdly, the metabolic control appears to be less fluctuating when the intermediately-acting insulin is given early than when regular insulin is employed until convalescence is reached. It is the authors' impression that patients can be stabilized rapidly and kept in control by this method.

Several studies[7,14,15] have compared the daily blood glucose curves obtained in patients receiving protamine insulin, globin insulin, and NPH insulin. The present observations have shown that 2 to 1 regular, and protamine insulin mixtures in a ratio of 2 to 1 produce blood glucose curves of the same duration and produce superior control of the postprandial blood glucose levels. This suggests that in the future protamine-zinc insulin may be largely supplanted by NPH insulin.

Summary and Conclusions. 1. The value of NPH insulin in the control of diabetic patients admitted to the hospital for the treatment of various

medical and surgical complications was studied.

2. The blood glucose curves indicated that NPH insulin was effective in the control of the postprandial blood glucose as well as the fasting glucose levels in the majority of these patients. In a few instances, it was necessary to deduct 10 to 15% of the carbohydrate from breakfast in order to avoid a high postprandial rise in blood glucose. This carbohydrate was given as an interval bedtime feeding. When this failed to effect a lowering of the post-breakfast sugar, a small dose of regular insulin was administered in the syringe with the NPH preparation.

3. NPH insulin is a valuable preparation for the control of diabetes in patients with medical and surgical complications, and possesses advantages not found in other unmixed insulin preparations.

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SERUM COMPLEMENT IN RHEUMATOID ARTHRITIS*

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THE original intent of this study of complement titer in rheumatoid arthritis was to find data that might prove valuable in our understanding of the role of immune phenomena in this disease. Various investigators in the past have provided data leading to the concept that such phenomena are important. The first of these was provided by Billings[1] in 1912, who pointed to the frequent occurrence of streptococcal infections of the upper respiratory tract in rheumatoid arthritis. Subsequently, Cecil[3] demonstrated in the sera of a large number of patients with well established rheumatoid arthritis a high titer of agglutinins against beta hemolytic streptococci. Later investigators[9,16] have reported on other abnormal agglutinating reactions of rheumatoid arthritis sera. These reactions have been identified as a property of the beta–gamma globulin portion of the blood proteins[11], and it is of possible significance that the major function of the beta–gamma globulins appears to be that of carrying the immune bodies of the blood[5].

It was, therefore, our original feeling that a study of the level of blood complement activity could possibly give us further information on the significance of these observations. If, during serial studies, we should observe falls in titer that correlated with disease activity, we might assume that these periods were marked by great antigen–antibody activity. This sort of *in vivo* "binding" of blood complement by antigen–antibody systems has been demonstrated in experimental anaphylaxis[14] and in various diseases known to be of allergic origin, principally acute nephritis[7] and serum sickness[13]. However, as will be evident, our studies do not show this phenomenon. On the contrary, they indicate that disease activity in rheumatoid arthritis is reflected by an *elevated* serum complement titer rather than a depressed titer. The effect of ACTH upon this titer has been of further interest to us.

Methods. COMPLEMENT TITERS. Complement titrations were done on morning fasting serum specimens, in each case the determination being made on the same day as the bleeding. The method is a modification of that described by Heidelberger[8]. The blood was allowed to clot at room temperature for the first hour, after which it was kept refrigerated until the actual determination. The

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50% hemolytic unit of complement activity is described as the amount necessary to produce hemolysis of half the cells in a system using 0.5 cc. of a 2% suspension of sensitized sheep cells, the cells being sensitized with 4 units* of rabbit amboceptor.

The unit of amboceptor is determined as follows: Serial dilutions of antisheep cell rabbit serum (amboceptor) are made in saline solution** and mixed in equal proportions with a 4% washed sheep cell suspension. To 0.2 cc. portions of these mixtures are then added 0.2 cc. of 1:40 high titer guinea pig serum, and the volume brought up to 0.8 cc. with saline solution. The tubes are incubated 40 minutes, after which that tube showing complete hemolysis in highest dilution is considered to have 1 unit of amboceptor. A dilution of amboceptor 4 times this in strength is said to contain 4 units of amboceptor, when used to sensitize an equal volume of 4% sheep red cells.

The sheep cells are stored in modified Alsever's solution[2]. Before use, they are washed 4 times in 10 volumes of saline solution, then brought to approximately 4% by suspending in 24 volumes of saline solution. This is then exactly adjusted to 500,000 cells per c.mm. (4%) by hemolyzing 0.25 cc. portions with 5 cc. of distilled water and so adjusting that the amount of hemolysis gives a reading of 186 on the Klett-Summerson photoelectric colorimeter. The density of this cell suspension can be checked at intervals by an ordinary red cell count. The cell suspension is then sensitized by mixing it with equal volumes of amboceptor. The mixture is allowed to stand at least 10 minutes at room temperature before use.

To 0.5 cc. portions of these sensitized cells are added 0.5, 0.6 and 0.75 cc. portions of suitable† dilutions of the unknown serum, the volume adjusted to 2 cc., and the whole incubated 40 min. at 37° C. along with controls for nonspecific hemolytic and anticomplementary effects. At the end of this time, the tubes are removed from the bath, diluted to 6 cc. with saline solution, the non-hemolyzed cells centrifuged off, and the degree of hemolysis in the supernatant fluid recorded on the Klett. This is converted to percent hemolysis by comparison with the average of 3 tubes showing complete hemolysis with distilled water. From these values is calculated the value of the function $\frac{y}{1-y}$, where y equals percent hemolysis and the function is obtained from von Krogh's formula[15] describing the lysis of red blood cells by an immune system. The y values are $\frac{y}{1-y}$ then plotted on logarithmic paper against the volumes of serum dilution used. These 3 points fall on a straight line, and where this line crosses the value for $\frac{y}{1-y} = 1$ (this being the value for 50% hemolysis), one can read off that volume of serum which would give exactly this degree of hemolysis. By definition such a volume of serum dilution would have exactly one 50% hemolytic unit of complement activity, and simple arithmetical calculations allow one to express this strength of complement activity as 50% hemolytic units per cc. of original undiluted serum. Normal values generally fall between 80 and 150 units. It is noteworthy that in following any particular serum, fluctuation in its complement value of ±10% can be normally expected but beyond this range is usually abnormal.

Sedimentation Rates. Sedimentation of red blood cells is reported as sedimentation index (normal 0.35), indicating the fastest rate of fall per minute in the Wintrobe tube. The method is that of Rourke–Ernstene[12].

Choice of Test Subjects. As normal controls, healthy young men and women, primarily hospital personnel, were chosen. The rheumatoid arthritis patients represent a random choice of patients from the Robert Breck Brigham Hospital and the Peter Bent Brigham Hospital. Some of these had had their disease for many years, others for only a few months. All, however, had such active

* 5 units of amboceptor were used for a short time with no apparent difference in the calculated complement titers.

** 8.5 gm./L. NaCl, 0.575 gm./L. barbital, 0.375 gm./L. sodium barital, 0.595 gm./L. $MgCl_2.6H_2O$, 0.0137 gm./L. $CaCl_2$.

† Preliminary "rough" titrations are done on each new serum in order to determine what dilution of the serum will be optimal for the subsequent, more exact "50% hemolysis". To 5 tubes containing 0.2 cc. portions of 1:10, 1:20, 1:30, 1:40, and 1:60 dilutions of the serum are added 0.2 cc. of the sensitized sheep cells, the volume adjusted to 0.8 cc. with saline, and then incubated at 37°C. for 30 min. The tube showing 100% hemolysis is noted and from an arbitrary, predetermined scale the proper dilution for the 50% hemolysis is picked.

processes as to bring them to the hospital relatively incapacitated.

Results. In Fig. 1 is presented the range of complement titers in our normal controls and in patients with rheumatoid arthritis. It will be seen that of 35 normals, only 1 had a titer above 150, and only 4 had titers above 130. On the other hand, among 31 rheumatoid arthritis patients, there were 10 with titers above 150, and 14 with titers above 130. The lower limit index is a much more sensitive method for measuring disease activity than is the complement titer.

The course taken by the complement titer in serial studies is illustrated in 6 cases of rheumatoid arthritis in Fig. 3. The patients were followed under the relatively constant conditions of prolonged hospitilization. They received the usual course of physiotherapy given to all patients. Gold, arsenic, and spray irradiation therapy were used

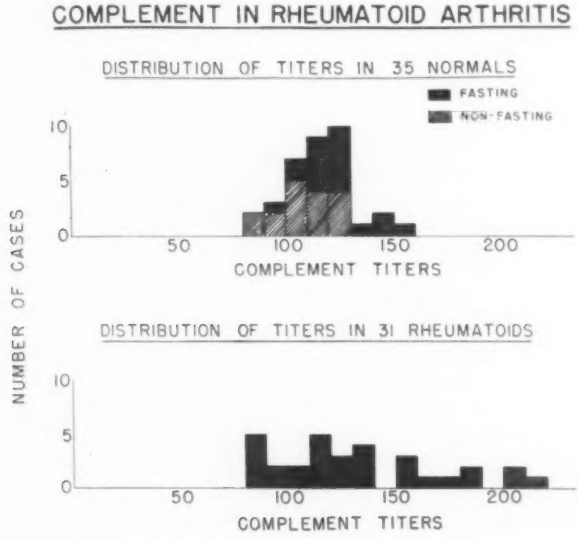

FIG. 1.—The range of complement titers in normal subjects and in patients with rheumatoid arthritis.

of complement titer was the same in both groups, 80 units.

That the complement titer does not parallel the sedimentation rate as an index of disease activity is shown by the data plotted in Fig. 2. It will be noted that since the upper limit of normal for the sedimentation index is .35, almost all the sedimentation rates are elevated. However, only a third of the complement titers are elevated above the value of 150. Therefore, one would conclude that the sedimentation

as adjuncts in therapy in three instances (F.F., V.S., and P.T., respectively), but in none of these was it felt that there was a specific effect of these methods of treatment upon the disease process. Titers were performed on each patient from 2 to 4 times a week. In no instance was there noted a specific fall in serum complement titer which could be interpreted as evidence for disease activity. In one instance (F.F.) there was a peaked rise in serum complement titer follow-

ing a biopsy under general ether anesthesia. This elevation completely subsided in the course of 12 days. In the patient F.H. a smaller but more prolonged rise in complement titer was observed on the 33rd and 44th days of observation. This rise could not be correlated with any change in his clinical activity. Also it was felt that this rise was barely beyond the limits of the usual variation in titer that we have observed with our method of assay of complement activity.

The effect of ACTH on complement titer in 6 other patients, each of whom was given one or more courses of therapy, is illustrated in Fig. 4 and Table 1. In all but one, the course of

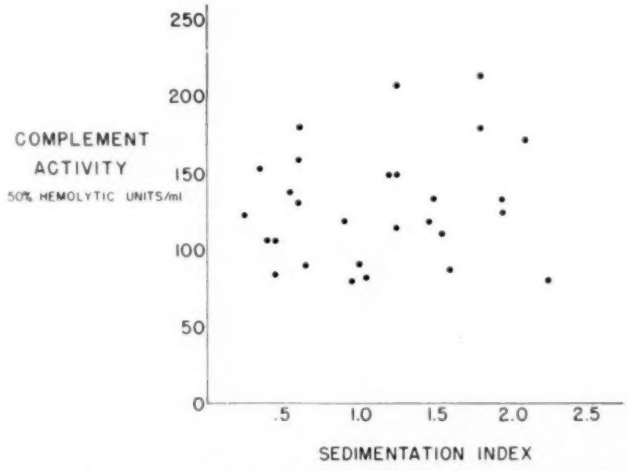

FIG. 2.—The failure of the complement titer to correlate with the sedimentation rate in rheumatoid arthritis.

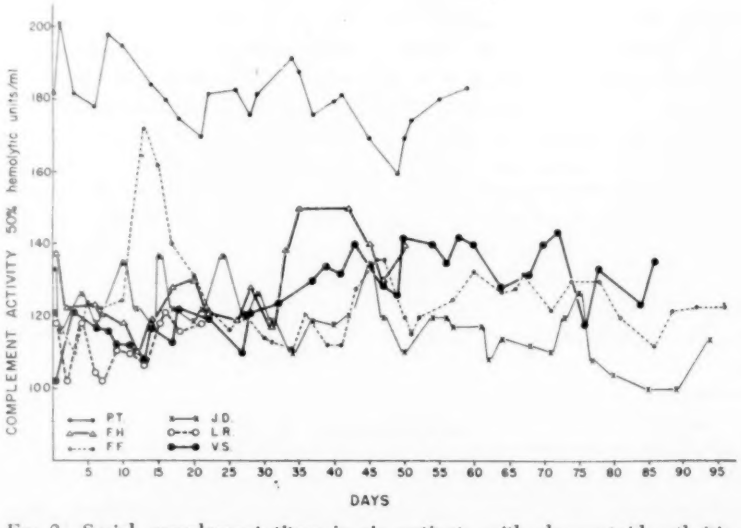

FIG 3.—Serial complement titers in six patients with rheumatoid arthritis.

ACTH therapy lasted 3 weeks. It is evident from an examination of the curves that there is a tendency for complement titer to fall during this treatment. Furthermore, as illustrated in Fig. 5, there was often an abrupt rise in complement titer immediately following ACTH therapy, with the rebound lasting about 10 days before returning to lower values again. This occurred in 5 of the 6 instances in which the depression of the complement was 30 units or more.

TABLE 1.—THE EFFECT OF ACTH THERAPY ON COMPLEMENT TITER IN RHEUMATOID ARTHRITIS

	Titer		
Patient	*Start*	*End*	*Change*
H. C.	180	110	−70
E. A.	100	45	−55
H. A.—1	210	170	−40
—2	180	150	−30
—3	125	88	−37
E. B.—1	120	120	0
—2	135	150	+15
—3	174	122	−52
B. G.	86	100	+14
A. N.—1	82	97	+17
—2	87	74	−13

Numbers designate 50% hemolytic units/ml.

Discussion. Our studies confirm the finding of Rachmilewitz and Silberstein[10] that rheumatoid arthritis is a disease which is not associated with demonstrable depression in complement titer. On the contrary, there is a definite tendency for these patients to have titers higher than normal. This last is in keeping with recent studies by Fischel[6], who has emphasized the importance of such rises in complement titer in various active pathological states.

The extensive study by Ecker[4] in 1946 on complement activity in infectious diseases revealed the presence of low titers in many of these cases, but the frequency of elevations above normal was also clearly pointed out. Furthermore, he fractionated the complement activity into its four major components and showed that in those instances where lowered complement activity was present, there was a loss of "combining" components only. On the other hand, where the total titer was elevated, he found that all the components of complement joined in the elevation. Therefore, it would seem that in those active disease states there were two forces operating, those tending to lower total complement titer by binding the "combining" components, and those tending to raise the total titer by elevating all the components. Neither Ecker's nor Fischel's studies, nor those of our own, shed light on the means whereby such elevation in total complement titer may occur. However, one might assume teleologically that it represents a nonspecific mobilization of forces that might be protective for the organism against challenging agents. This easy explanation fails completely, however, to clarify the specific mechanisms involved.

In view of our finding that complement titer tends to be elevated in rheumatoid arthritis, it is not surprising to find that ACTH therapy often is associated with a falling titer. One might expect this fall merely as a consequence of the reduction in the disease activity. The rather striking rebound of titer in the immediate posttreatment period would suggest a rapid return of the active disease state. Furthermore, one is immediately struck by the similarity between the spike in the case of F.F., after her biopsy under ether anesthesia, and the spikes that characterize these post-ACTH-treatment periods in several instances. The possible stress factors at play related to the biopsy are easily appreciated.

Yet there are certain data which suggest the possibility of there being a direct effect of ACTH on comple-

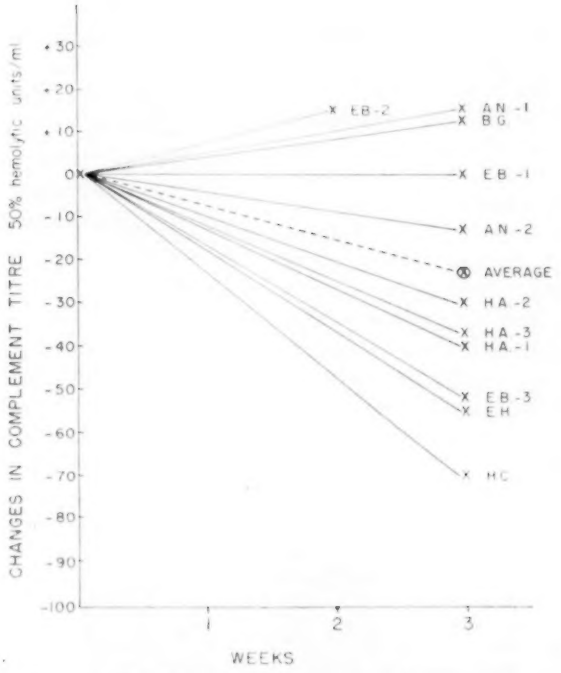

FIG. 4.—The effect of ACTH on complement titer.

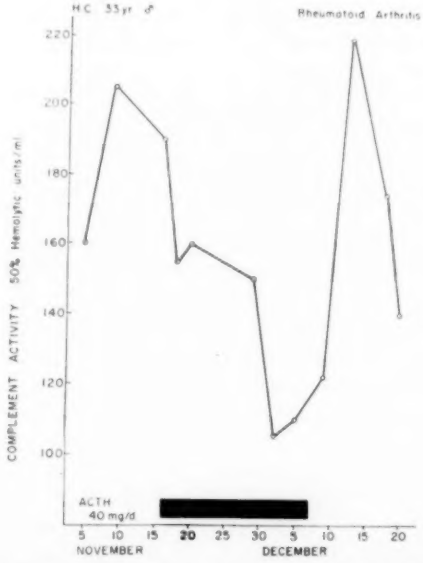

FIG. 5.—Complement depression and rebound in rheumatoid arthritis treated with ACTH.

ment protein, perhaps that of inhibiting its manufacture. For instance, the rather striking rebound of complement titer in the immediate post-treatment period is not maintained, but tends promptly to fall off again to lower levels (Fig. 5). This would not be expected, if the rebound were due entirely to return of disease activity. Also the fact that in the case of E.A. (Table 1) there was a fall in complement titer to values well below anything we have seen in normal healthy subjects is more easily explained, if one assumes a direct effect of ACTH on complement activity. The answer to this question will come only when the opportunity presents itself to follow serially the complement titer on a series of normal healthy subjects.

Summary. 1. Rheumatoid arthritis is a disease often characterized by an elevation in serum complement titer.

2. The complement titer does not parallel the sedimentation rate as a measure of disease activity in rheumatoid arthritis.

3. ACTH therapy in rheumatoid arthritis is associated with a falling complement titer in a significant proportion of cases.

ACKNOWLEDGEMENT. The authors are grateful to Mr. Jack Kasarjian and Miss Elizabeth Geiler for the invaluable technical assistance that they gave.

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THE USE OF A CATION EXCHANGE RESIN IN THE MANAGEMENT OF THE FLUID RETENTIONS OF NORMAL AND TOXEMIC PREGNANCIES: PRELIMINARY REPORT

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The earliest sign of an impending toxemia of pregnancy is an excessive gain in weight due to fluid retention. This is produced by a retention of electrolytes, principally sodium, and water. Apparently there is an increased tubular reabsorption of sodium in the kidney, which creates a positive sodium balance. This retained ion is stored in the extra vascular space with its bound water. The exact mechanism which initiates this pathological condition is unknown, but it has been shown conclusively that if the sodium intake is restricted, the syndrome of fluid retention can be prevented or reversed. But low sodium diets are rather unpalatable, and it is exceedingly difficult to convince asymptomatic young pregnant women that it is necessary for them to restrict their dietary sodium intake. Because they rarely heed the physician's advice, hospitalization is frequently necessary to protect them and to instruct them in the preparation and use of a low sodium diet.

Recently organic chemical agents, the cation exchange resins, used commercially for years, have been introduced into medicine. These agents permit the patient to ingest sufficient sodium to satisfy the need for a palatable diet, yet prohibit its absorption in the gastrointestinal tract. The resin used in this study, Resodec*, is the potassium and ammonium form of a cross-linked, polyacrylic (polycarboxylic) cation exchanger. Its active exchange centers are thus carboxylate radicals which are attached to the surface of the resin. The attraction between the resin and various cations is based on the size and electrical charge of these cations, as well as on their concentration. Since the molecular weights of potassium and sodium are similar, the differential exchange is based on the relative concentrations of the two ions. The exchange power of the resin becomes active at a pH of 6 and attains maximum capacity at a pH of 14. Because potassium is the only element, other than sodium, which is removed from the gastrointestinal tract in significant amounts by the resin, this ion is added in sufficient quantity to compensate for the loss. The ammonium ion is added in order to provide maximum palatability and also to act as a mild diuretic.

It has been reported by Hay and Wood[2] that fecal sodium levels rise greatly, and urinary sodium levels diminish greatly, following the administration of this potassium–ammonium resin. Moreover, reporting a private communication, these authors indicate that in rats the resin showed no toxicity through 2 generations, nor any appreciable fecal loss of trace metals; in humans, preliminary clinical work indicates that the resin does not interfere with the utilization of vitamins. Reportedly, acidosis is not met except in

* Resodec was supplied by Smith, Kline, and French Laboratories, Philadelphia, Pa.

patients with severe renal damage[3].

The binding capacity of this resin is approximately 4½ to 5 milli-equivalents per gram. The usual daily dose of 45 gm. supplies about 2½ gm. of ammonia, which is equivalent to the administration of 8 gm. of ammonium chloride.

Method. In this study healthy young pregnant women with fluid retention were admitted to the hospital. History and physical examination revealed no primary vascular or renal disease in this group. Tests of serum total protein and A/G ratios were performed on every patient in order to eliminate the possibility of the edema being due to hypoproteinemia. No such cases were found. In addition the following determinations were made: uric acid, 24-hour urines for protein and sodium, complete blood counts, urine analyses, measurements of fluid intake and output, and daily weight. After a 24-hour control period the investigation was started. The resin was given orally mixed with fruit juice in doses of 15 gm. 3 times daily with meals. The patients did not complain of its taste. No undesirable side effects were noted.

In order to evaluate the action of the resin accurately, the patients were divided into 3 groups. Group 1 was the control group in which 2 ambulatory patients were placed on hospital diets containing 2 gm. of sodium, and were *not* given resin.

Group 2 consisted of 7 ambulatory patients who were placed on hospital diets containing 2 gm. of sodium and *were* given the resin.

Group 3 consisted of 2 ambulatory patients who were placed on a hospital diet with 6 to 9 gm. of sodium, and *were* given the resin.

The patients' progress and response to the resin were followed by daily measurements of weight, urine output, and urinary sodium excretion.

Results. GROUP 1. (CONTROL GROUP). The 2 patients in this group both followed the same clinical course. They had small weight losses and at the termination of the study there was still evidence of edema. The following case illustrates this:

A 23-year old nullipara, gravida i, was 34 weeks pregnant when admitted, with a normal blood pressure (120/60), urine negative for protein, and pitting edema up to the knees. She had gained a total of 12¾ pounds. She was placed on a 2 gm. sodium diet with no resin and was permitted to be ambulatory. The results of her regimen appear in Table 1.

During the low salt regimen, the patient lost a total of 6¾ pounds, 4¾ pounds of which were lost in the first 24 hours of hospitalization. After this immediate loss, her weight remained rather stable. As noted above, she remained in a positive sodium and fluid balance throughout the testing period. Her sodium intake had been restricted but not to the level required for fluid mobilization; therefore, at the termination of the experimental period she still had edema. This demonstrates rather clearly the necessity for a rigid reduction in oral sodium intake if edema fluid is to be mobilized solely by this method.

GROUP 2 (2 GM. SODIUM INTAKE WITH RESIN). The seven patients in this group all showed significant weight losses, marked urinary diuresis, progressively lower daily urinary sodium excretion, and the mobilization of all clinical edema. The following case demonstrates these changes:

A 22-year old para i, gravida ii, was 32 weeks pregnant, with a total weight gain of 16½ pounds, edema up to the knees, blood pressure 130/74, and urine negative for protein. She was placed on a hospital diet including 2 gm. of sodium, was ambulatory, and was started on Resodec after an initial 24-hour control period. The results appear in Table 2.

This patient lost a total of 13½ pounds in 8 days. She had a marked diuresis, and the sodium content of her urine decreased significantly daily. At the termination of the study there was no clinical evidence of edema. In this instance the bulk of the orally ingested sodium apparently was bound by the resin and excreted in the feces. This patient demonstrates the practical value of the resin in the management of fluid retention. Sufficient sodium was permitted in the diet to make the food palatable, yet the resin prohibited its absorption. After the resin was stopped, the patient gained 1¼ pounds in 6 days, probably indicating a slight tendency toward fluid retention on a 2 gm. sodium intake.

GROUP 3 (6-9 GM. SODIUM INTAKE WITH RESIN). The 2 patients in this group followed the same clinical pattern. The course of one of these,

selected as an example, is summarized as follows:

A 29-year old para i, gravida ii, was 38 weeks pregnant, with a total weight gain of 28 pounds, 2+ edema, blood pressure 120/80, and a protein content of 150 mg. in a 24-hour specimen of urine. She was permitted to be ambulatory, was placed on a hospital diet containing 6 to 9 gm. of sodium, and was started on the resin after an initial 24-hour control period. The results appear in Table 3.

On the unlimited sodium diet with the Resodec, there was an increase in urinary sodium output and essentially no weight loss.

TABLE 1

Date	*Weight*	*Fluid Intake*	*Urine Output*	*Sodium Intake*	*Sodium in Urine*
3–9	184	1314	500	86.9 mEq./24 hr.	98 mEq./24 hr.
3–10	179¼	720	1000	" " "	87 " "
3–11	—	1320	750	" " "	42 " "
3–12	179¼	1620	2550	" " "	45 " "
3–13	179	1620	2500	" " "	48 " "
3–14	178¼	1560	950	" " "	45 " "
3–15	179¼	1080	800	" " "	39 " "
3–16	179	1410	900	" " "	
3–17	178¼	1290	700	" " "	

TABLE 2

Date	*Weight*	*Fluid Intake*	*Urine Output*	*Sodium in Urine*	*Remarks*
3–8	216½	900	2000	195 mEq./24 hr.	
3–9	210½	2190	3380	114 " "	Resodec started
3–10	208½	1380	2530		
3–11	—	2140	2200	67 " "	
3–12	206	1060	2525	23 " "	
3–13	205	2166	2550	22 " "	
3–14	203½	1560	2300	5 " "	
3–15	203½	1800	1900		Resodec stopped
3–16	203½	2400	2175		
3–17	203½				
3–18	204½	2160	2200		
3–19	204½	1975	2150		
3–20	205	780	640	18 " "	
3–21		1920	2400	18 " "	
3–22	205				

TABLE 3

Date	*Weight*	*Fluid Intake*	*Urine Output*	*Sodium in Urine*	*Remarks*
2–22	192				Unlimited Na
2–23	192			99 mEq./24 hr.	
2–24	189½				Redsodec started
2–25	190				
2–26	190½	2930	2550		
2–27	191½	2410	3400		
2–28	190	2850	1300	182 mEq./24 hr.	
3–1	192¼	2550	1450		
3–2	191½	2940	1250		
3–3	191¼			211.2 mEq./24 hr.	Resodec stopped
3–4	195½	2760	2500		
3–5	194½	700	1550	72 mEq./24 hr.	400 mg. Na
3–6	191¼	2210	1750		
3–7	190	1730	2400		
3–8	189½	1530	1550		
3–9	188½	2040	3740	127 mEq./24 hr.	Delivered
3–13	178½				
3–14	178½				Discharged

As soon as the Resodec was stopped, however, the patient gained 4½ pounds in 24 hours. Her sodium intake was then reduced to 400 mg.; and during the next 4 days, she lost 6 pounds. This demonstrates that, with an unlimited sodium intake, Resodec is not capable of binding all of the alimentary sodium; a certain amount is absorbed. The 4½ pound weight gain in the 24 hours after the Resodec was stopped can be attributed to increased sodium absorption and fluid retention. The 6 pound weight loss on the 400 mg. sodium diet further demonstrates the value of the very low sodium diet and shows very clearly that the resins are not necessary in the management of fluid retention if the patient can adhere to a 400 mg. sodium diet.

Conclusions. Eleven patients with fluid retention of pregnancy were treated with a cation exchange resin (the resin was not used in the treatment of pre-eclampsia or eclampsia). From this investigation it appears that this resin permits the daily ingestion of 2 to 3 gm. of sodium, with the simultaneous mobilization of the excessive fluid which was retained in the tissues. No fluid mobilization was achieved with the resin when the patient's ingestion of sodium was unlimited, nor was fluid mobilization seen when the patient was sustained on the 2 gm. sodium diet without the resin. Therefore, it appears that Resodec is a valuable addition to the present regimen and may prove to be of greatest value in the management of the fluid retentions of pregnancy in outpatients who refuse to adhere, or find it difficult to adhere, to low sodium diets.

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PULMONARY INFARCTION: A FREQUENTLY MISSED DIAGNOSIS

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AND

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The diagnosis of pulmonary embolism and infarction is not so simple as most of us have been led to believe. Alleged to present a rather typical and consistent syndrome, it is, to the contrary, often quite atypical and the condition is frequently overlooked. It is the purpose of this paper to call attention to these atypical cases in the hope that clinicians will become more alert in the recognition and consequent treatment of this too often fatal occurrence.

Reimann, writing in Cecil's "Textbook of Medicine,"[25] states that the signs of pulmonary embolism with infarction are: sudden piercing pleural pain, dyspnea rapid in onset, cough with small hemoptysis, cyanosis, tachycardia, sweating, fever, and leukocytosis. He further describes physical findings to be localized friction rub and moist râles. Less than a paragraph is devoted to reminding readers that not all cases present these symptoms. The majority of medical textbooks and other published literature offer equally brief comment concerning cases of pulmonary infarction which do not present the "typical" picture[12,29].

Fatalities in Undiagnosed Infarction. Within recent months the authors have observed the deaths of 2 patients who succumbed without a definite diagnosis being made antemortem to explain their death. Necropsy showed both to have massive pulmonary emboli with extensive infarction of lung tissue. In each case the symptoms, or rather lack of symptoms, obscured the diagnosis even in retrospect. These cases are presented here briefly:

Case 1. L. C. (167352) was a 50-year old white female who was seen by her local physician at her home and referred here for study. Her chief complaints were easy fatigability and weakness of several months' duration.

Her past medical history was negative and there were no symptoms referable to any special body system. Physical examination was normal as were laboratory studies. Roentgenograms of the chest and gastrointestinal tract were normal. The electrocardiogram was interpreted as normal. On the 4th hospital day the patient was told that she could go home the following morning. Tentative diagnosis was psychoneurosis.

On the morning of the 5th hospital day the patient told a nurse she felt short of breath even while at rest. A resident physician saw the patient and she had no complaints except mild dyspnea. Physical examination, including careful survey of the legs, was negative. Temperature was 99° orally and pulse was 110. She was seen later in the day by her attending physician and again no cause could be found for her complaint. Although it was felt that she was apprehensive or excited about going home, it was decided nevertheless to keep her another day for observation. She slept fitfully with mild sedation. Nurses on early morning rounds found the patient dead in bed. Diagnosis was deferred.

Postmortem examination showed a large embolus occluding the pulmonary artery supplying the right middle and right lower lobes with resultant massive infarction. There was no evidence of other organic disease. The heart was normal, as was the brain. No origin for the embolus was found and it was as-

sumed to have arisen in the lower extremities.

CASE 2. D. B. (427634) was a 70-year old white male with a 3-year history of exertional dyspnea and attacks of mild anginal pain. He was admitted to the hospital for rest and evaluation. Complete examination was essentially normal except for evidence of generalized arteriosclerosis. His first 4 days in the hospital were uneventful.

On the morning of the 5th hospital day of partial bed rest he told the intern he felt very tired but had no specific complaints. The following morning he still had fatigue, and anorexia also. A careful physical examination and a 2nd electrocardiogram were normal. He was seen frequently and was examined twice daily, but there were no other symptoms and no significant physical findings. He died quietly 3 days after his initial complaint. The only significant finding was an elevation in the white blood cell count from 10,000 to 17,000 and a slight elevation in pulse rate to 100 per minute.

Necropsy showed a pulmonary embolus with extensive infarction. The coronary arteries showed some narrowing but no occlusion. A small nodule in the prostate was found to be malignant but no metastases were seen. Again the origin for the embolus was not found and again was assumed to be from the legs.

Analysis of Postmortem Examinations. These unfortunate experiences prompted this investigation. It includes a review of all cases of pulmonary embolism with infarction which were necropsied in the University of Michigan Hospital over the 10-year period between 1940 and 1950. A total of 124 cases was available out of 4203 postmortem examinations. This number included only those in which it was reasonable to suspect embolism with infarction as the immediate cause of death. It does not include a much larger number of cases in which 1 or more small pulmonary infarcts were found but which appeared to be merely incidental. Of this group of 124 cases, 104 were selected as having histories, progress notes, and other studies sufficiently complete to give a clear picture of the patients' course.

While the primary object was to study the atypical cases, a brief general discussion is also included of the entire problem.

Little agreement is found in the medical literature on this subject. It is safe to say that pulmonary embolism is a much more common occurrence than is generally thought. It has been reported by various authors as occurring in from 1 to 5% of all autopsies. Hunter[14] reports 3.1%; Kirby[18] reports 5% in all postoperative cases; and others give figures in the same range[36]. Despite advances in recognition and treatment, the incidence is actually increasing, according to Rubin[29]. This increase is probably due to 1) advancing age of the population; 2) more surgical procedures in the aged, and 3) more industrial and automobile accidents with severe trauma to bones and deep body structures.

It is a disease of later life with the vast majority occurring in persons over 40 years of age. Obese persons are more susceptible, and cardiac and postoperative patients are likely victims. There is no predilection to either sex. The age and sex distribution in the present series are shown in Table 1.

TABLE 1. AGE AND SEX DISTRIBUTION IN 104 CASES OF INFARCTION

Age	*No.*	*Sex*	*No.*
< 20	11		
20 to 30	5	Male	54
30 to 40	19	Female	50
40 to 50	39		
> 60	30		

While most reports list elderly postoperative patients as leading the list of casualties, Hampton[11] reports 370 autopsied cases with only 40% in surgical patients, 30% in cardiac patients, and 30% in noncardiac subjects. To show the high incidence of simple phlebothrombosis, which may of course lead to embolism, Rössle[27] performed 400

autopsies with examinations of the deep veins of the leg and found 27% of all patients over 20 years of age had such involvement.

ORIGIN OF EMBOLI. Most emboli causing infarction in the lungs arise from the deep veins of the legs. Hunter reports that 45% of all fatal pulmonary emboli arise from the legs. Bauer[3] goes further with phlebographic studies and reports that 98% of all thrombi of the legs originate in the veins of the calf muscles. Allen[1] states that 95% of emboli come from leg veins. Whatever the true percentage is, it can be said that most emboli of consequence do arise from the legs. There are, in fact, few other venous sources from which an embolus large enough to occlude a pulmonary artery can arise. The chambers of the heart and larger pelvic veins must, of course, be considered. The origin of fatal emboli in the present series is shown in Table 2; in cases in which a definite location was not found the origin has been attributed to the legs. This assumption could be challenged, but unfortunately routine dissection of the extremities is not practiced in this country.

TABLE 2. ORIGIN OF EMBOLI IN 104 CASES

Origin	%
Lower extremities	61
Mural thrombi in right side of heart	24
Iliac vessels	9
Inferior vena cavae	3
Bladder and perivesical region	2
Hemorrhoidal	1
Total	100

SITE AND TYPE OF LESION. The location of infarction in the lungs is of interest and is shown in Table 3. Some observations have been made with experimental emboli in an effort to see if there was a predilection to certain lung fields from different sites of origin. Steinberg and Mundy[33] used lead shot in the jugular veins of animals and found that while there was no preponderance to either lung the majority of emboli found their way to the middle and lower lobes. Smith and Abernathy[32] used lycopodium spores and clumps of tubercle bacilli in serum as emboli and selected different sites of injection with their rabbits in varying positions. They found that emboli from the upper portion of the body tended to lodge in the upper lobes and that the lower lobes were usually involved when the origin was in the lower portion of the body. They postulated an incomplete mixing of the blood from the inferior and superior vena cavae which produced a layering effect causing such a distribution. Their results, however, do not enable one to locate the site of origin by knowing the site of injury in the lungs. Suffice to say that, in the present series, the majority of lesions were in the lower lobes with the right middle lobe next in frequency.

TABLE 3. DISTRIBUTION OF PULMONARY EMBOLI IN 104 CASES OF INFARCTION

Lobes involved	*Number of cases*
Right lower	27
Left lower	19
Right middle	11
Left upper	10
Right upper	6
Multiple	31

Not all emboli produce infarction. Occlusion of a major branch of the pulmonary artery causes instant death in many instances and edema of the lungs will be the only pathological finding[29]. Occlusion of medium-sized vessels is found to cause most infarcts. It should be remembered, however, that many small infarcts are not incompatible with life, and often the involved lung parenchyma is restored through collateral bronchial circulation

or recanalization[33]. In fact, infarction is said not to occur unless the general circulation, including the bronchial blood supply, is embarrassed, that is, with such conditions as cardiac decompensation and general debilitation[2,6,31].

The cause of death with pulmonary embolism and infarction is not clearly understood in many cases, but reflex vasoconstriction of the pulmonary arterial bed through sympathetic nervous control is important[29]. Complications such as further cardiac failure, pneumonia, and abscesses also contribute.

Pathological studies show "stuffing" of the lung parenchyma through distention of the alveoli and capillaries with red blood cells and degeneration of corpuscular elements and coagulative necrosis of alveolar walls[4,21].

TABLE 4. CLINICAL DIAGNOSIS RECORDED AS CAUSE OF DEATH IN 104 CASES OF INFARCTION

Pulmonary infarction	44
Congestive heart failure	14
Myocardial infarction	6
Pneumonia	6
Bronchogenic carcinoma	5
Cerebrovascular accident	5
Congenital heart disease	4
Subacute bacterial endocarditis	3
Rheumatic heart disease	2
Lymphoblastoma	1
No diagnosis	14
Total	104

Diagnosis. The diagnosis of pulmonary embolism and infarction may at times be exceedingly difficult because of the absence of signs and symptoms or the resemblance to many other acute clinical conditions. It has been said that the diagnosis of pulmonary infarction will be made in direct proportion to the index of suspicion of the physician[3,12]. To illustrate the difficulty and mistakes made in diagnosis, Table 4 shows the final clinical impressions recorded in this series of patients shown later at autopsy to have massive pulmonary infarction. In fairness to the clinicians it should be explained that the diagnosis of pulmonary infarction was considered in many of these patients, but this chart records only the primary clinical diagnosis listed as the immediate cause of death.

Conditions other than the above which may be mistakenly diagnosed as pulmonary infarction are acute abdominal episodes, mediastinal emphysema, spontaneous pneumothorax, bronchiectasis, and breast pain in women.

The classical picture of pulmonary embolism and infarction has been mentioned in the early part of this report. From 104 cases the authors saw only 15 with these "typical" findings. In 14 of the cases of this series none of the so-called classical findings were present, that is, pleural pain, hemoptysis, dyspnea, and friction rub. Table 5 summarizes the occurrence of the well known triad of symptoms: hemoptysis, dyspnea, and chest pain.

TABLE 5. SYMPTOMS IN 104 CASES OF FATAL PULMONARY EMBOLISM

Dyspnea only	21
Pain and dyspnea	20
Hemoptysis and dyspnea but no pain	17
Hemoptysis, dyspnea, and pain	15
Shock, "sudden death"	10
Hemoptysis only	7
None of above symptoms	14

The physical findings related to this condition also may be quite misleading but are usually more helpful to the clinician in making the diagnosis if he is alert to the possible significance of minor abnormalities. Rapid heart action, mild dyspnea, and reduced blood pressures are often early manifestations of pulmonary embolism and infarction. These are expressions of vasomotor shock and may or may not be accompanied by other signs. Syncope is not uncommon in pulmonary embol-

ism and may be the first and only clue. The most consistent finding in this series was an elevation of pulse rate. This was present in over 60% of these cases. Râles were found to be the 2nd most common physical sign. The "classical" friction rub was found to be present in only 9 of the 104 cases. The authors feel that the occurrence of friction rub is probably more common than this figure indicates, but friction rubs are often transient and one must listen at the opportune moment. Table 6 shows the frequency of the various physical findings. In 10 cases there were no abnormal chest findings and in 6 cases there were no abnormal physical findings whatsoever.

TABLE 6. PHYSICAL FINDINGS IN 104 CASES OF FATAL PULMONARY EMBOLISM

Abnormality	*Number*
Pulse rate increase	60
Chest râles only	35
Dullness and râles	25
Temperature elevation	18
Dullness in chest only	10
Decreased breath sounds	9
Friction rub only	7
Friction rub and râles	2
Localized leg pain	5
"Shock" without special signs	3
No abnormalities	6

Laboratory studies are important and may, in fact, be the only abnormal finding. Leukocytosis was by far the most common and helpful finding in this series and this is recorded in Table 7. Increased sedimentation rate and elevated bilirubin levels are known to accompany pulmonary infarction in many instances.

The early picture may be one of primary shock with none of the signs and symptoms on which a diagnosis of pulmonary embolism and infarction may be made. Three patients presented a picture of severe shock. In addition 5 had a diagnosis of cerebrovascular accident as the cause of death. It has been pointed out by Roth[28] that the leading symptoms in those cases which resemble cerebrovascular accidents are due to severe hypotension with resultant cerebral anoxemia.

The presence of pulmonary embolism and infarction should always be suspected and carefully searched for in patients who are generally not responding well to treatment. Again this is of prime importance in elderly bedridden patients, both medical and surgical. These patients often have a sense of impending disaster and will be uneasy but cannot give a reason[26]. Younger persons with rheumatic heart disease and auricular fibrillation are also susceptible to embolism as pointed out earlier by one of us[20] when it was shown that pulmonary embolus was the most common immediate cause of death in these patients.

Gold[10] has stated that frequent and careful physical examinations and questioning of all patients would lead to many diagnoses of this condition now being overlooked. The old adage, "a diagnosis never considered is never made", was never more applicable than it is to this problem.

TABLE 7. LEUKOCYTE VALUES IN 104 CASES OF FATAL PULMONARY EMBOLISM

Range	*No. of Patients*
0 to 5,000	4
5,000 to 10,000	21
10,000 to 15,000	28
15,000 to 20,000	34
Over 20,000	17
Total	104

Another line of investigation which offers promise for early diagnosis of thrombotic and consequent embolic phenomena is found in the work of Cummnie and Lyons[7]; Sandrock and Mahoney[30] and Kay *et al.*[17]. They in-

vestigated the presence and levels of certain constituents of the blood involved in clot formation. If such tests are found practical, their use could lead to the early recognition of states that are compatible with incipient thrombus formation.

ELECTROCARDIOGRAMS. Most cardiologists and internists agree that the electrocardiogram is seldom of significant assistance in the diagnosis of pulmonary infarction. The cardiologist is rash indeed who will make a definite diagnosis of pulmonary infarct from an electrocardiogram alone. As with Roëntgen-ray examination, it is, and can be, suggestive and confirmatory only. In this series of cases 15 out of 37 electrocardiograms taken were reported as being compatible with pulmonary infarction.

The electrocardiographic changes are produced by acute dilatation and strain upon the right heart, or the so-called acute cor pulmonale. According to White[34] and others, the characteristic pattern shows prominence of S waves in lead I; Q waves in lead III; and low to slightly inverted T waves in lead II and in the 2nd of 6 precordial leads or low to inverted T waves in lead IV.

Wilson[35] states that to assist in the diagnosis of pulmonary embolism with infarction the electrocardiogram should be taken within a few hours of the accident while acute dilatation and strain are present. It is recognized that the changes produced are transient and will be missed unless the tracing is made at the opportune time. Johnston[16] insists that evidence of right bundle branch block be present before he will agree that pulmonary embolism is suggested by the electrocardiogram.

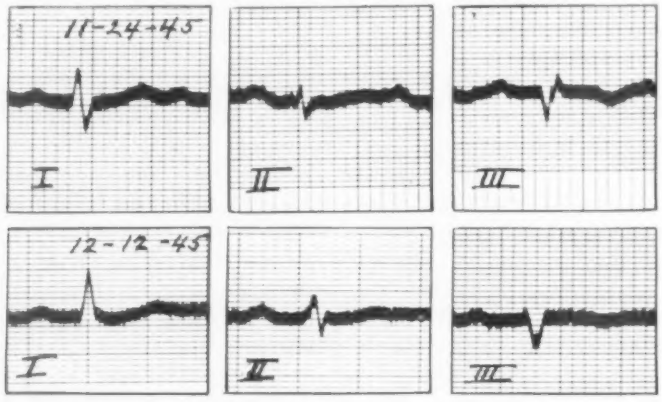

FIG. 1.—The electrocardiogram as seen in pulmonary infarction, when tracing is taken at opportune moment, is shown in the 3 leads on the top line. A follow-up tracing is shown on the 2nd line with complete disappearance of the abnormalities. Only with the appearance and disappearance of such changes can the cardiologists say an electrocardiogram is compatible or suggestive of pulmonary embolism.

Other changes may also be seen, especially in elderly patients with histories of coronary insufficiency. In these patients a picture of myocardial ischemia or even myocardial infarction may be present. Chronic cor pulmonale will also give changes to be distinguished from those of acute cor pulmonale caused by pulmonary embolism.

Bryant[5] states that the presence of tachycardia alone, without known cause, must be viewed with suspicion, and that in many postoperative patients later proved to have had pulmonary emboli it has been the only electrocardiographic change.

A tracing with changes typically produced by pulmonary embolism is shown in Fig. 1. It should be repeated that a tracing of this type can be reported as "compatible with" and not diagnostic of pulmonary embolism.

ROENTGENOGRAMS. Roentgenograms offer a valuable aid in the diagnosis of pulmonary infarction, but here again it usually gives confirmatory or suggestive evidence only. In relatively few cases will radiologists report a chest film as showing an outright infarct of the lung. Their reports, too, are usually worded as "compatible with" or "suggestive of pulmonary infarction."

TABLE 8. ROENTGENOGRAMS IN 50 PATIENTS WITH PULMONARY EMBOLISM

Compatible with pulmonary infarct	7
Pneumonia	10
Congestion	7
Pleural effusion	5
Parenchymal abnormalities undifferentiated	10
Normal	11

In the series reviewed 50 roentgenograms of the chest were made after the patient became ill with what was later proved to be pulmonary infarction. Only 7 of these were reported to be pulmonary infarction. In fairness, however, it should be stated that many of these were bedside films which were of a quality not sufficiently clear to bring out details or minor changes. Others were reported as congestion, pneumonia, fluid, and hazy densities of unknown etiology. Table 8 shows the Roentgen-ray interpretation made on these patients. It should be remembered, however, that pulmonary infarcts are often complicated by congestion, pulmonary edema, abscess, and pneumonia. It should also be realized that changes noted in roentgenograms may not be evident for several days following lung injury.

The monumental work of Hampton and Castleman[11] in 1940 contributed much to the interpretation of chest findings by correlating immediate postmortem chest roentgenograms with autopsy findings. They arranged to secure 7-foot chest films of 370 patients immediately after death with autopsy following. This study probably added more to the knowledge of direct relations of changes shown by Roentgen rays and anatomical changes than any other. They concluded that there is no typical Roentgen-ray finding with pulmonary embolism and infarction. They state that massive infarction even may show no change except minimal pleural fluid. Infarcts, when evident, are sharp in outline, and these outlines will show on film if Roentgen rays are projected through the greatest thickness of the infarct. Suffice to say, the film changes are seldom of the wedge shape alleged to be typical.

Radiologists do believe, and rightly so, that they are often able to discover suggestive evidence of infarction not known to the clinician. Their suspicions should certainly be heeded by the physician at the bedside and every effort made to confirm this suspicion and start treatment as indicated.

Prevention and Treatment. The treatment of pulmonary emboli with infarction falls into two inseparable classes—prophylactic and active. Since the almost universal acceptance of anticoagulant therapy these 2 divisions have become overlapping in many instances but by no means completely so.

Probably the most important aspect of prophylactic therapy is for the physician to keep always in mind the possibility of such a complication. Elderly patients confined to bed, cardiacs, postoperative patients, and unfortunately the majority of bed-ridden patients, should be carefully followed with this always dangerous mishap in mind. All such patients should be examined at least twice daily, on morning and evening rounds, for signs of early phlebitis. Patients should also be carefully questioned in regard to chest pain, dyspnea, and cough. Above all, any elevation in pulse rate, temperature, or white blood count should be eyed with much suspicion until a definite cause can be determined.

Ochsner[23] emphasized prophylactic treatment with a program of early ambulation, deep breathing exercises, ankle extension exercises, frequent change in position, and general measures to prevent hypotension and slowing of the circulation. Avoidance of heavy sedation, constipation, and abdominal distention is also advised. Desiccated thyroid has been given by some in the hope that circulation would be speeded. This last idea, how-

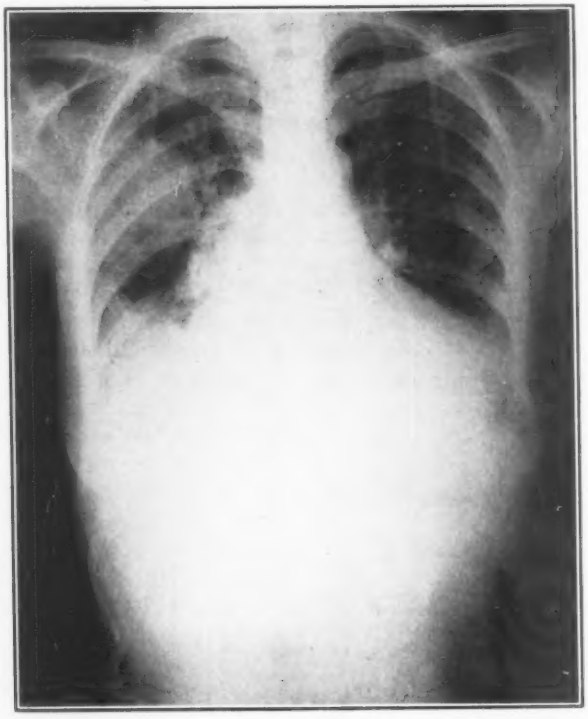

FIG. 2.—The roentgenogram above, taken on a 60-year old white female, shows changes proved at autopsy to be a result of pulmonary infarction. The radiologist reported this as suggestive of pulmonary infarction and also pointed out that it could be due to pneumonia, congestion, neoplasm, atelectasis, or other causes. While this picture does suggest a wedge shape, it cannot be called definitely diagnostic. The patient also had rheumatic heart disease to complicate further the diagnosis for the radiologist.

ever, has now been discarded by practically all physicians.

Powers[24] reported 1519 cases of major surgery with early ambulation postoperatively. He concluded that while the incidence of thromboembolism was not reduced, the fatal emboli were only ½ (0.5%) that of a similar group with ambulation at a much slower rate.

Before anticoagulant therapy was in use, the favorite method of treatment, both prophylactic and active, was venous ligation, usually of the superficial femoral veins, but also at times to include the iliacs and inferior vena cavae. These measures, while still in use, are not performed nearly so frequently as they were 5 years ago. Lillie, Buxton, and Duff[19] critically reviewed all cases of thromboembolism over a recent 9-year period and concluded that, while venous ligation still held a place in treatment, the use of anticoagulants was much preferred in the vast majority of cases. It was further concluded by Lillie *et al.* that venous ligation was definitely indicated in cases where anticoagulants were undesirable because of bleeding or concurrent disease where these drugs were dangerous (subacute bacterial endocarditis, leukemia, aneurysms, etc.). For safe dicoumarin therapy it is also *imperative* that adequate facilities be available for determining the prothrombin level. Combined therapy with venous ligation and anticoagulation, or the changing from one treatment to another, is sometimes necessary when thromboembolic disease progresses subsequent to one form of treatment, or if anticoagulation therapy must be stopped because of any of the reasons listed above or for further surgery. The dosage and treatment program using anticoagulants and/or venous ligation is covered carefully and completely elsewhere[8,9]. In regard to anticoagulant therapy alone, Murray[22] reports excellent results with intravenous injection of heparin given promptly after an embolus or infarction is diagnosed. He reports a series of 149 patients with pulmonary infarction with no fatalities, whereas 20% of his control group died.

De Takats and Fowler[8] advocate the immediate use of atropine and papaverine to reduce vasospasm and bronchospasm. This allegedly allows the patient to survive with the aid of collateral circulation until other therapy can be instituted.

Pulmonary embolectomy has been practiced by some thoracic surgeons, most commonly in the Scandinavian countries. Other measures, but none the less important, such as oxygen, general supportive and shock-combating treatment, are frequently advised.

In the authors' opinion one of the most promising methods of treatment is prophylactive anticoagulant therapy in all patients considered particularly susceptible to thromboembolism. Although this plan of treatment is still in the experimental stage, it does appear from early reports that such a program reduces the incidence of embolic phenomena. Duff and Linman[9], Harvey and Finch [13], and others have reported such series with encouraging results. It must be admitted, however, that as yet no completely satisfactory method either of prophylactive or of active treatment has been found.

Summary and Conclusions. 1. Attention is called to the many instances of pulmonary embolism with infarction which do not present the "typical" clinical picture and are consequently misdiagnosed. All autopsies over the past 10-year period were reviewed from records at this hospital, a total of 4203.

2. It was found that only 15% of the cases selected presented the "typical"

picture as described in most textbooks. An almost equal number was found to have died with this complication without any really conclusive symptoms or signs.

3. A general review, from the authors' experience and from the literature, is presented with emphasis on the many aspects of this disease which might aid the physician in the diagnosis and treatment of pulmonary emboli with or without resultant infarction.

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EVALUATION OF A SIMPLIFIED THROMBOPLASTIN EXTRACT

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Anticoagulant therapy has become the accepted method in the treatment of thromboembolic diseases. Dicumarol is still the anticoagulant most widely used. It exerts a hypoprothrombinemic effect which is determined by measuring the rate of prothrombin conversion. More specifically, the one-stage method of Quick and those tests with modifications of Quick's original method are the ones most frequently used[1,2].

These tests of prothrombin conversion are dependent upon uniform constituents, with one exception, namely, thromboplastin. Each prepared batch of thromboplastin varies in potency, and, in storage, even under ideal conditions, undergoes changes in potency. To simplify the test, increase its accuracy, and eliminate dangers resulting from inaccurate tests of prothrombin conversion, a thromboplastin with the following properties is desirable: 1) stability under ordinary conditions of temperature for an indefinite period of time; 2) ease of preparation; 3) extraction which is not costly or laborious, thus eliminating many possibilities of errors; 4) a readily discernible end point with plasma; 5) usable immediately by the addition of diluent only, thus eliminating the time-consuming and costly practice of extraction in each individual laboratory. Such a thromboplastin would eliminate weighing, the process of extraction, and the addition of calcium chloride. If this type of thromboplastin could be made available dicumarol could be used safely and readily in all hospitals and under circumstances which are now prohibitive.

In 1940 Souter, Kark, and Taylor[3], using the method of Flosdorf and Mudd[4], lyophilized a saline extract of fresh rabbit brain prepared according to the technique of Quick[2]. This dried material was kept at room temperature without loss of potency for 10 weeks. When the dried material was diluted to the original volume, a thromboplastin solution was obtained which was equal in strength to a freshly extracted one. This is in contrast to freshly extracted thromboplastin which, when stored at room temperature, begins to lose potency within several hours.

A desiccated thromboplastin extract containing ionizable calcium and sodium chloride has recently been investigated in our laboratory.* To this thromboplastin is added distilled water and this reconstituted extract is then ready for use in the usual prothrombin tests. The desiccated thromboplastin gives a sharp end point both with whole plasma and the dilute 12.5% plasma. It possesses all the properties

* Prepared under the name Simplastin by Chilcott Laboratories, Division of the Maltine Co.

of the ordinary form of thromboplastin which is extracted daily, plus the most desirable property of stability under changing temperature conditions.

Methods and Results. Normal plasma in our laboratory at 37.5°C. had a whole plasma prothrombin time of 16.8 seconds, plus or minus 1 second, and the 12.5% plasma had a prothrombin time of 42.0 seconds plus or minus 2.5 seconds with desiccated thromboplastin. Serial dilutions of normal plasma were made so that the concentrations ranged from 10% to 100% plasma, and the prothrombin test was performed on these plasmas with ordinary as well as the desiccated thromboplastin extract. The results of this comparison showed that desiccation caused no loss of potency, as seen in Fig. 1. Neither did it produce any unusual properties in the thromboplastin which would have become evident in serial plasma dilutions. Desiccated thromboplastin extract was stored under the following conditions for 21 days: 1) room temperature, 20° to 26.5° C.; 2) 4° to 5° C.; 3) —5° C.; 4) 37.5° C. This is represented graphically by Fig. 2. Variable temperature conditions had no noteworthy effect upon desiccated thromboplastin extract when the prothrombin test was performed on normal and dicumarolized plasma. Ordinary thromboplastin loses its stability within a few hours when stored under similar conditions.

Two batches of desiccated thromboplastin were compared with one batch of ordinary rabbit lung thromboplastin by performing the prothrombin test on dicumarolized plasma, as shown in Fig. 3. The results of this comparison illustrate that the different batches of desiccated thromboplastin can be produced with little or no variation in potency.

Lastly, desiccated thromboplastin extract was used to perform the prothrombin tests on patients receiving heparin and dicumarol for the treatment of thromboembolic diseases. I

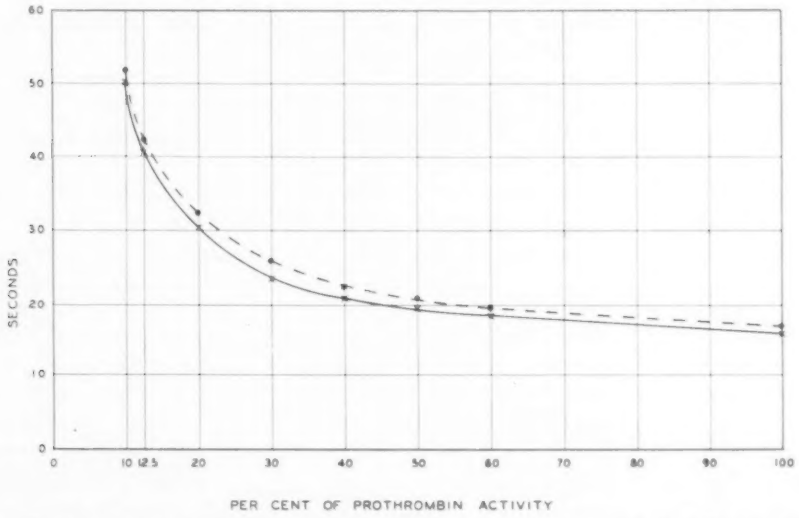

FIG. 1.—Prothrombin test performed on dilutions of normal plasma with ordinary thromboplastin (———) and with desiccated thromboplastin (— — — — —).

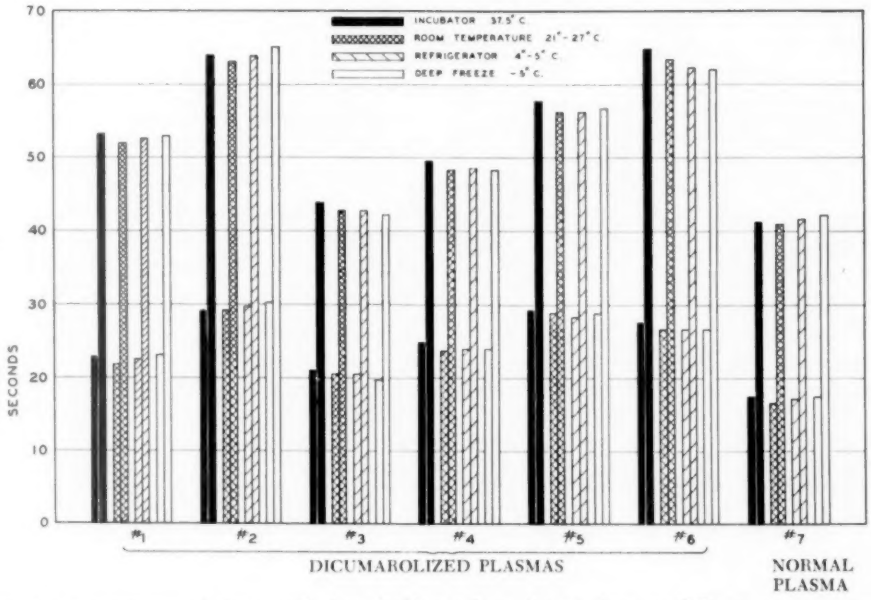

FIG. 2.—Comparison of desiccated thromboplastin kept for 21 days at different temperatures.

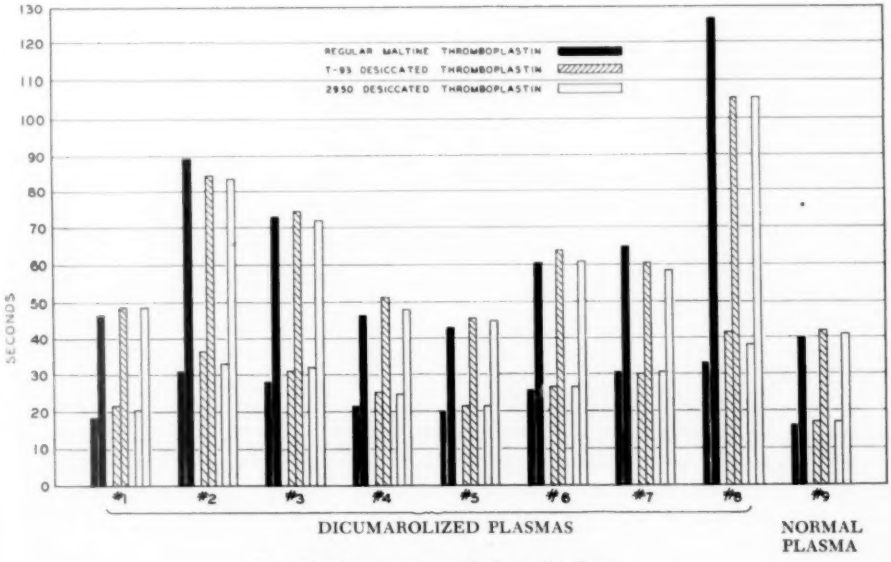

FIG. 3.—Comparison of thromboplastins.

was found as adequate as ordinary rabbit lung thromboplastin. This extract is now used by the authors in performing all prothrombin determinations in their laboratory. From these results dicumarol dosages are determined. It has been found that a prothrombin time twice the normal whole plasma time and a prothrombin time twice the normal 12.5% plasma prothrombin time indicate adequate anticoagulant therapy with desiccated thromboplastin extract.

Conclusion. In producing hypoprothrombinemia for the treatment of thromboembolic conditions, the desiccated thromboplastin extract is believed to be the thromboplastin of choice in performing the one-stage prothrombin test. It possesses consistent stability at variable temperature conditions for prolonged periods of time. Because of the nature of this desiccated thromboplastin extract, many costly and cumbersome steps are eliminated in preparation for the performance of the test. This leads to greater accuracy and simplicity, and should therefore be found invaluable by the clinician who treats thromboembolic diseases.

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PROGRESS
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AN INQUIRY INTO THE SURGICAL TREATMENT OF ULCERATIVE COLITIS*

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IT is now 76 years since Wilks and Moxon[74] declared that the dysenteries of ancient and evil repute held within them a form of colitis with characters of its own. They wrote in 1875, "The term colitis is sometimes used as synonymous with dysentery. Our usual language has indeed been too indefinite, nay, incorrect, in speaking of all affections of the large intestine as dysenteric; for the true dysenteric process, although in many features like simple ulcerative colitis, yet is a disease having certain definite characters." This statement is justly credited with being the origin of the entity now known as chronic idiopathic ulcerative colitis, though it was not a new thought. The same Wilks in 1859, according to Saundby[63], had expressed the opinion that the word "dysentery" did not cover all forms of ulceration of the colon. In the succeeding years clinical studies have mounted in volume from the single case report of Allchin[1] in 1885 to a report published in 1950 embracing the life histories of 2000 patients seen at the Mayo Clinic in the years between 1918 and 1937[64]. The natural history of the disease is known, save for its origin. There is, then, a measure to test the agents and plans of therapy that have been employed.

Medical management has had the longest trial. Its basic concepts have altered little through the years, though

* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

the specific chemicals and biologicals have changed with the times. Indeed, "Treatment unfortunately appears to have very little effect on the disease. Absolute rest in bed with slop diet and opium, and hot fomentations if the pain and diarrhoea are very severe, probably afford the best chance, but the prognosis is exceedingly grave." So wrote White[73] on medical management in 1895. With some refinements and a less grave prognosis the program is acceptable today. By contrast surgeons have 3 times changed their basic concepts of therapy. Their first was to assist the physician to irrigate more efficiently the colon by proximal colostomy; then to divert completely the intestinal contents from the inflamed colon by transverse ileostomy; and finally, to cure by colectomy. A bold and aggressive attitude toward the treatment of ulcerative colitis is in evidence among surgeons of experience in this disease. It has risen in intensity over 2 decades to culminate in the successful total removal of the diseased colon at 1 operation for the relief of exsanguinating hemorrhage[48]. It is reflected in the plea that ileostomy and colectomy be performed earlier in the course of the disease before complications and irreversible organic changes occur, and that these separate operations be often combined into one. Are the surgeons merely taking advantage of modern technical skills? Or is the welfare of the patient really enhanced thereby? The reluctance of the physician to recommend surgical therapy for his patient with ulcerative colitis has its origin in 2 beliefs borne out of past experience. One is that the immediate operative mortality is unreasonably high; the other, that the patient with an ileostomy must suffer a handicap greater than the disease had enforced. Can these beliefs now be justified? It is proposed to examine into all aspects of the surgical treatment of ulcerative colitis; its indications, its expectations, its hazards, and its fulfillment to the end that its place in the present day management of chronic ulcerative colitis may be made clear.

The Accomplishments of Medical Management. It has been recognized from the first clinical descriptions of the disease that ulcerative colitis is primarily a medical problem. Handicapped by ignorance of the etiology and by the lack of a specific agent for treatment, a system of medical management has evolved aimed at securing remissions, preventing relapse, and restoring metabolism to normal. As Kiefer and Jordan[45] have stated, like peptic ulcer, medical management of this disease must recognize the propensity to relapse so that no patient can be considered permanently cured while he is still alive and has his colon. It is pertinent to discover what medical management has accomplished in the way of preservation of life and the prevention of disability from complications of the disease. It may be argued that the figures to be given are misleading since they represent experiences only among the more seriously ill who have needed hospitalization at least once, and ignore perhaps the majority of patients with ulcerative colitis. That may be true, for the actual incidence of the disease is not known. For the purpose of this discussion the argument is not valid since it is in this very group that surgical treatment has its indications and must show its worth in comparative values.

The disease has carried with it an inevitable mortality and a less well appreciated but high degree of invalidism in its survivors. The death rate in the earlier years of recognition was frightful. White[73] stated in 1895 that the prognosis was extremely grave. In fact, he said there was no convincing evi-

dence that recovery from the disease was possible. Allchin[2] gathered 177 case reports of ulcerative colitis from 3 London hospitals for the period 1883 to 1908 and found that 55% had died. There has been recorded a steadily declining mortality ever since due to more effective control of associated metabolic disturbances, and the appearance according to hospital records of less severe forms of the disease. Mortality rates of the present day are represented by the 5% of McKittrick and Moore[54], the 11% of Kirsner *et al.*[46], and the 17.3% of Warren and Sommers[71] in a collected series of 1200 cases. Bockus[10] says it is doubtful if the mortality due to ulcerative colitis should exceed 10% of those afflicted even including those with the acute fulminating form of the disease. And there is a late mortality. Dennis[30] reported a 12-year survey of 72 patients in which there was an initial mortality of 20%, but 50% were dead in 5 years, and 66% were dead at the end of 10 years. The most important study of this type is that of Sloan, Bargen, and Gage[64] upon the life histories of 2000 patients. The average age at the time of diagnosis was 34 years and the average age at the onset of the disease was 4.7 years earlier. There was a 20-year survival of 56% but a normal calculated 20 year expectancy of life from age 34 of 83%. The most frequent causes of death are peritonitis from free perforation of the colon, pneumonia, "toxemia", inanition, hemorrhage, carcinoma, nephritis, vascular thromboses, and abscess of the liver and lungs[10,46,64].

Disability from this disease, in spite of good medical management, is great in terms of chronic invalidism, loss of time from work, inability to hold employment, annoying symptoms, curtailment of normal social activities, impoverishment by long periods of hospital care, and periods of mental depression. Physicians of lesser experience and those less sensitive to their patient's way of life do not appreciate the handicaps imposed by the disease ulcerative colitis. Buzzard, Richardson, and Turner[16] studied 68 survivors of 116 patients who had been treated over a period of 2 to 12 years. Only 12 were considered to be normal. They observed that although 80% were leading useful lives, nevertheless 80% were in fact afflicted with symptoms. Elsom and Ferguson[33] made a comparative study of patients treated by medical and surgical means with a 1 to 12 year follow-up. Of 23 in the medical group there were only 14 survivors of whom but 2 were free of the disease, and 1 of these was totally crippled by arthritis. The 12 remaining patients were all under constant medical supervision, 6 having had recurrences, 3 were complete invalids, and not 1 was capable of full productivity. In an evaluation of the medical management of ulcerative colitis Kiefer[44] found that among 327 cases followed from 2 to 15 years the results were satisfactory in 46% and unsatisfactory in 54%. He concluded that in the milder forms the disease can be controlled in approximately two-thirds of the cases, while in the more severe forms only one-third can obtain satisfactory results. Further, he believes that the remaining patients who are poorly controlled must either accept more or less disability, chronic invalidism, or death, or submit to surgical treatment. Kirsner *et al.*[46] present a more hopeful picture in their study of the clinical course of ulcerative colitis in 100 patients selected for completeness of data, length of period of observation, and accurate information on present status. It was concluded that 6% were in a permanent remission, and that 47% were being maintained in a "satisfactory" state of health. As an illustration of the eco-

nomic burden imposed by this disease, 37 of the above 100 patients were in the hospital from 100 to 300 days, and 5 were hospitalized from 458 to 662 days. The causes of disability are evident if one thoughtfully examines a list of complications that have been observed to occur in the natural course of the disease[10,14,60]. Surgeons are challenged by these causes of death and the complications that lead to invalidism or complete disability. They believe surgical techniques provide the means of preventing these deaths and minimizing or abolishing the complications leading to disability. In fact, the only cure for the disease now possible is colectomy. Payment is exacted in terms of an operative mortality, surgical complications early and late, loss of the colon, and permanent ileostomy. Is the price too great?

On The Surgical Treatment of Ulcerative Colitis. HISTORICAL. The surgeon was early called to assist the clinician in the management of these patients. In the belief that the colitis was an infectious process and that the products of inflammation remaining in the colon were a source of poisoning by absorption, the surgeon was asked to provide a proximal vent through which the entire colon might be efficiently washed many times a day. The vent also offered a means of applying healing remedies to an inflamed mucosa. Stone[65] attributes the first cecostomy to Boas in 1903. In 1895 Keith[43] performed a right inguinal colotomy which he closed 1 month later after having attained success. With Weir's[72] introduction of appendicostomy as "a new use for the useless appendix" the 3 surgical methods of providing for simple and direct colon irrigations were complete. These methods were fast losing favor by 1920 but had 1 last advocate in Kunath[47] as late as 1936.

The idea that diverting the fecal stream from the inflamed colon might favorably influence the disease may be credited to the physician White[73], though he suggested that a high colostomy might in addition be used for flushing. This concept apparently gained adherents, for in discussing Allchin's paper[2] of 1908 Meakins emphasized this diversion as most important. Lockhart-Mummery violently disagreed. About this time ileosigmoidostomy was applied as a diversionary measure, championed as late as 1925 by Rienhoff, Jr.[61]. As a result of dissatisfaction with each of the above named procedures, and appreciating the value of rest to the colon in certain ulcerative and obstructive lesions, J. Y. Brown[13] described in 1913 a technique of ileostomy by division and closing of the distal end. This marks the beginning of the modern operative treatment of ulcerative colitis. After learning that ileostomy offered a measure of control of the disease and that man could live in health without function of his colon there followed an exploration of the possibilities of cure by colectomy.

The origins of colectomy in the management of ulcerative colitis are obscure. It is difficult to assign the concept or the first performance to one source. In a discussion of Garlock's[39] paper Cave pays tribute to the courage of Howard Lillienthal who, in 1900, performed colectomy and ileosigmoidostomy for this disease. Papers by Logan[51], Yeomans[76], and Strauss[66] all mention colectomy as having been done, probably with restoration of bowel continuity. Payne[58], Rienhoff, Jr.[61], and Jones[41] indicated a preference for ileostomy over colectomy because the latter was too formidable. The first total colectomy of record for this disease is that reported by Strauss, Friedman, and Block[67] in 1925. The

present day use of colectomy for the cure of the disease and the rehabilitation of invalids appears to have been initiated by Rankin[9,59] who gave indications for colectomy and who demonstrated that total colectomies were not "formidable". He advocated the 3 stages in common use today: ileostomy, partial colectomy, proctosigmoidectomy. From this time, 1930, there has been a more widespread use of surgical methods as the indications have broadened and become more sharply defined, as the operative mortality has decreased, and as the "ileostomy" patient has ceased to be regarded as accursed.

Indications For Ileostomy. With few exceptions, ileostomy is the first procedure to be considered when surgical treatment is undertaken on any patient with ulcerative colitis. It is a momentous decision, for once made there is rarely any turning back. Instead, it is likely to be only the first step in 1 or more operations that will result in the irrevocable loss of a part or all of the colon, with the patient dependent upon his ileostomy for the maintenance of life.

From a review of the literature it is impossible to provide a uniformly acceptable set of criteria for the selection of cases for operation. The vagaries of the disease are such that the classification of the types of disease is not uniform and its phases are named and defined at the convenience of each author in the light of his own knowledge, experience, and prejudice. In consideration of the indications for surgery let it be clearly understood that ulcerative colitis is universally considered to be a medical disease, and that no such patient is a candidate for surgical treatment without trial of good medical management. The only possible exceptions are the emergency states of acute perforation of the colon and massive hemorrage. The proportion of patients that have been judged to have complications or sequelae requiring surgical treatment varies widely, from 5.5%[8] to 39%[55], with an average of about 25%[27,36,49]. The proportion will be higher, of course, when hospital patients alone are under consideration. Those indications commonly employed will be discussed under two headings to point up the time allowed for decision.

Urgent Conditions. 1. *Acute Fulminating Disease.* This may be the initial attack or it may be a virulent exacerbation of the chronic disease. It is the most controversial of the surgical indications, for the mortality is greatest in this phase regardless of the type of treatment. It was natural that ileostomy should be tried in this desperate circumstance, usually as a last resort. Mortality figures for ileostomy must be read in this light, and deaths on the medical service will be correspondingly lower for this type of the disease as the responsibility is shifted to the surgeon. Unfortunately, comparable rates on medical and surgical treatment of this phase are not obtainable. Advocates of ileostomy have been Dennis[27], Garlock[40], Cave and Thompson[23], and the Lahey group[25,45]. The last have consistently urged ever earlier ileostomy before the patient must succumb to his disease regardless of operation, and before irreversible tissue changes have occurred. They are willing to accept a relatively high mortality, though not rightly charged to surgery, in order to salvage a few. As one chooses to operate earlier in the course of the fulminating disease he passes the point at which he can tell certainly whether the patient must die without ileostomy, or whether operation will ever be necessary. As Cave[20] has pointed out, it is a difficult decision to make and there is a temptation to deny the indication

because of the excessive mortality as have Ault[3] and Brown, Gleckler, and Jones[12]. McKittrick and Risley[55] state that in general few of these patients have been saved by ileostomy but admit of exceptions. In any event, intensive medical treatment is given a trial to determine if a remission may be expected. Cattell and Sachs[19] suggest that this trial last from a few days to a week. At least the trial period should have a definite limit, at the end of which a decision for or against operation must be made[54]. Experience at the Graduate Hospital has convinced Bockus[10] that ileostomy should not be done in acute fulminating disease; since discontinuing ileostomy in these cases medical deaths have been only 10%. It is difficult to find mortality statistics of comparable value for ileostomy limited to this indication. They will vary from 23% to 50%[8,12,23] and perhaps higher[45].

From the evidence presented in published reports, one may conclude that the mortality of ulcerative colitis is the greatest in this phase of the disease, regardless of the type of management, that surgical treatment by ileostomy has not proved its superiority over medical management, that surgeons are divided in opinion as to the place of surgery in the acute fulminating phase, and that ileostomy has appeared to be life saving in some instances. Clinical judgment for or against ileostomy in a given circumstance must rule at this time. Reference will be made later to the use of colectomy in this phase.

2. *Hemorrhage.* Massive hemorrhage has the reputation of being a rare but highly lethal complication, in spite of Ricketts and Palmer's[60] statement that it is frequent but never fatal. Surgeons have given it the most concern and, except for a rare dissent[3], urge it as an emergency requiring surgical treatment. Most commonly this is ileostomy, though experience has shown it to be unsure in the control of severe bleeding[36,54]. Direct attack on the colon itself had not been recommended because of the prohibitive mortality of colectomy in these severely ill patients[19]. Ferguson and Stevens[36] and McKittrick and Moore[54] now urge ileostomy first followed by colectomy promptly if the hemorrhage is not controlled. This is Lahey's attitude backed by a report of successful total colectomy in this circumstance[48]. In view of the demonstrated failure of ileostomy to control massive hemorrhage from the colon in ulcerative colitis, and as consistent with surgical principles in the control of hemorrhage, it would seem best to proceed with colectomy as the initial procedure. There will of necessity be a high mortality rate, but lives will be saved thereby.

3. *Acute Perforation.* The same boldness now exhibited in the treatment of hemorrhage is apparent in the approach to the problem of free perforation of the colon. It is seldom mentioned as an indication for surgery because the patients are desperately ill and operative procedures in the presence of spreading peritonitis have enjoyed a bad reputation. To indicate the prevailing impression concerning the prognosis of this complication a quotation is taken from Bockus[10], "There is no single finding, with the exception of carcinoma or perforation, which justifies a hopeless prognosis in every case." Cattel and Sachs[19] also are resigned to the utter failure of either medical or surgical treatment if perforation and peritonitis have occurred. This is in support of their plea for ever earlier ileostomy in the acute fulminating disease designed to prevent perforation. Ferguson and Stevens[36] decry this attitude and express an opposite view in that they consider many of these

desperate cases too sick for anything but surgery. They present 2 case reports in which not only free perforation but massive hemorrhage was present simultaneously. In one, these complications followed upon ileostomy and were successfully treated by colectomy. In the other, emergency ileostomy was performed but the bleeding continued, though the perforation sealed, and emergency colectomy was successfully accomplished. McKittrick and Moore[54] agree that immediate ileostomy should be performed but go no further. Ault[3] believes this indication should be abandoned. In the light of modern surgical management and the evidence of successful colon resections in the presence of severely complicated disease[36,49,57], a further trial of this radical method of treatment is in order.

4. *Impending Perforation.* Dennis[27], Cave[21], Garlock[40], and Cattell and Sachs[19] all present this indication with little definition. At times, while a patient is under medical management an acute phase appears with signs of increased inflammatory activity in the colon and peritoneal irritation which may be interpreted as meaning "impending perforation." Most authors do not mention it, probably because it is intimately associated either with the acute fulminating phase or as a part of the intractable phase, and therefore considered under these headings. It is too ill defined to bear separate consideration.

5. *Obstruction.* Localized or diffuse cicatrix may result in obstruction which demands prompt relief by surgical means.

ELECTIVE CONDITIONS: 1. *Intractable Disease.* By definition this means not easily controlled or cured and is the most simple and accurate title that can be given this indication that has the widest of interpretations and sends the most patients to surgery. To Kirsner *et al.*[46] it means the persistence of severe symptoms during medical treatment. To Cattell and Sachs[19] it is failure of medical management so that the patient is unable to pursue normal activity or gainful occupation. McKittrick and Moore[54] describe a patient with intractable disease as one who is chronically ill, a semi-invalid, although ambulatory, and unable to carry on with the normal activities for one of his or her age, and who, in spite of good care, continues to have recurring acute or subacute exacerbations requiring frequent hospital admissions. To Ferguson and Welty[37] intractability means failure to show improvement on an adequate medical program, as measured by no fever, no sign of abdominal distress or colon irritation, restoration of weight lost, and ability to work and lead an essentially normal life. Colcock[25] best expresses the viewpoint of the Lahey group toward this less well defined but most frequent indication. "If a patient, in spite of careful medical management, is unable to carry on a reasonable degree of social and economic activity as a result of poor nutrition, weakness, abdominal or rectal discomfort, or uncontrollable diarrhoea, he should be advised to have an ileostomy with or without a subsequent colectomy." He further states that it should be considered and usually should be advised for any patient no longer able to continue productive work and who is incapacitated for 3 months out of the year. In speaking of medically intractable cases Bockus[10] recognizes the continuous type with universal colon involvement as the most difficult problem. He expresses concisely the reluctance of physicians to recommend surgery for intractability in these words, "The thought of a permanent ileostomy in a highly sensitive patient and the high mortality following ileostomy and colectomy have caused us to withhold oper-

ation in many such cases and often a state of inactivity of the disease has been achieved." The one negation of this almost universally accepted, albeit elusive, indication comes from Bargen, who stated in a discussion of the report by Cattell and Sachs[19], "I have frequently said that intractability is directly proportional to the physician's patience and long suffering. Intractability is rarely, if ever, an indication for surgical treatment." Later discussion will show that the views of Bockus and Bargen are no longer tenable.

2. *Pseudopolyposis.* Polypoid projections from the colonic mucosa have long been recognized as a by-product of extensive inflammatory disease. They were named pseudopolyps by Woodward[75] in 1881, since they were inflammatory in nature rather than true adenomas. They occur in from 10% to 15% of patients with ulcerative colitis[14,60,68] and are usually but not necessarily associated with long-standing active disease[5]. As evidence of the latter, however, pseudopolyposis has consistently been given as a surgical indication. In the last 15 years attention has been centered upon the relationship existing between pseudopolyposis and carcinoma. That association will be discussed as one of the indications for colectomy.

3. *Severe Local Complications.* Abscesses and fistulas about the anus and rectum, and abscess from slow perforation of the colon are universally accepted as requiring surgical management. Ileostomy is an indispensable adjunct to the purely local surgical procedure. Recently, Lahey[49] and Cattell and Sachs[19] have re-emphasized that fecal incontinence, which occasionally results from anal inflammatory changes due to chronic diarrhea, should be made an indication for ileostomy.

4. *Systemic Complications.* These are more often included as evidences of intractability and may not in themselves be indications for ileostomy. Arthritis is an exception in this regard because it is one of the more common systemic accompaniments and leads to great disability if the colonic disease is unchecked[33,46]. Relief from the pain and swelling of early arthritis is often dramatic, and if control of the disease is obtained before bone changes occur, crippling disability will be avoided[19,25]. Ileostomy, in this instance, must be regarded as only a stage in the cure by colectomy. Bockus[10] summarizes well this paragraph in the statement that progressive arthritis or other severe medical complications traceable to a focus of infection in the colon may become a surgical problem.

5. *Segmental Disease.* Comprising from 5% to 15% of all cases of ulcerative colitis this group has a relatively higher proportion coming to surgery in the belief that the rather slow progression from right to left can be halted by surgical interference[26]. It is discussed under indications for ileostomy for convenience, and in sympathy with Dennis'[27] view that if any surgery at all is required, it is safest to begin with ileostomy. The more common procedure, however, is ileosigmoidostomy and partial colectomy in either 1 or 2 stages[19,26]. Crohn, Garlock, and Yarnis[26] believe that all but the most mild cases should be operated upon, and before the disease can progress to involve the rectum. The limits of resection must obviously be gauged by initial x-ray examination and gross inspection at laparotomy. In contrast to Dennis[27], who believes it is not possible to determine if any part of the bowel is normal by Roentgen-ray examination, Crohn *et al.*[26] state that roentgenographic localization of disease in the large bowel is very accurate. Cattell and Sachs[19] report the poorest results of treatment to be in this group because

of the unsuspected presence of disease beyond the limits of resection. Segmental disease remains, however, a valid indication for surgery in the necessity to halt spread of the disease and prevent complications[3,5,10].

Indications for Colectomy. Twenty years after Brown introduced transverse ileostomy it had become apparent that ileostomy performed only a limited function in the management of ulcerative colitis. It often relieved toxemia and brought on dramatic clinical recovery but it did not restore the colon to a functionally normal organ and the colon usually remained diseased[42]. The last 20 years have seen the surgeon's attention shift to colectomy as the desirable and perhaps necessary sequence of all ileostomies[49].

McKittrick and Risley[55] introduce their indications for colectomy in the following fashion: "Following ileostomy a patient will usually follow one of four courses: (1) There may be a prompt and complete disappearance of all signs and symptoms and the patient becomes and remains well indefinitely. (2) The initial response may be completely satisfactory for months or years but at some later time there is a reactivation of disease in the colon. (3) A few patients are helped but the relief from the disease is incomplete. They are better but not well. (4) Finally, there is a small group which shows no apparent benefit from the ileostomy. Such patients usually have the acute fulminating type of the disease which goes on to a fatal termination or belong to the group with massive hemorrhage for whom further aggressive surgery is indicated. If the objective of the surgical treatment of ulcerative colitis is complete physiologic or anatomic elimination of the disease, the indications for colectomy are relatively clear."

1. *Life Saving.* Massive hemorrhage and acute perforation of the colon have been discussed in the section on ileostomy. It has been shown that colectomy can be successfully performed in patients who surely would have died of these complications. The outlook is no longer so hopeless in these states. Recently, Gardner and Miller[38] have performed colectomy and ileostomy in 1 stage successfully in acute fulminating disease. In 4 instances it has been total colectomy in 1 stage without mortality. It is not a form of surgical management likely to come into general use for the nicety of judgement necessary in the selection of patients is not given to many, and the fine medical and surgical teamwork necessary for success is not always present. It is a hopeful demonstration, however, of courage and skill in the refusal to accept death as inevitable in certain of these cases, and acts from the sound premise that the only known cure of the disease is removal of the colon.

2. *Polyposis and Carcinoma.* In 1932 Boros[11] reported a case of carcinoma developing in ulcerative colitis and remarked that similar reports were scanty, though Bargen had found 20 such cases at the Mayo Clinic in the years 1916 to 1927. Until 1935 the Lahey Clinic[17] had not seen an instance of carcinomatous degeneration in ulcerative colitis, nor had it been seen at the Massachusetts General Hospital[53]. It is now recognized that carcinoma is a threat to any ulcerative colitis patient who has his colon and long standing disease. The stated incidence varies with the author's experience. In a collective review Lynn[52] found it reported in from 0% to 3.2% of cases, the latter the incidence at the Mayo Clinic. The Lahey group now report that carcinoma was found in 7% of the patients operated upon and estimate that it occurs in 30% of the patients

with the disease existing 10 years or longer. They now urge colectomy in long-standing ulcerative colitis to prevent the development of carcinoma[19,49]. Carcinoma occurs with apparently greater frequency in the very young[5]. It is of a particularly virulent type, often multiple in origin, treacherous because the early symptoms and signs are masked by those of the associated disease. Control or cure is infrequent[5,7,19,49].

The relationship of pseudopolyposis to carcinoma of the colon is not so clear. It has frequently been suggested that the pseudopolyp of inflammatory origin undergoes a transition to true adenoma and then progresses to malignant degeneration[15,24,69]. One infers that this is usually the reason in mind when pseudopolyposis is given as an indication for colectomy[35]. There is no solid support for this theory. Warren and Sommers[71] state unequivocally that these inflammatory tumors are least likely to undergo neoplastic transformation and that no convincing case of this has been found. They further state that carcinoma develops in these patients by 1 of 2 processes: Either from neoplastic mucosal polyps to the same degree as in the general population, or from regeneration of mucosal epithelium that proceeds until precancerous epithelial hyperplasia develops. True adenomas are found either separately or in association with pseudopolyps[24,35]. Some 60% of the colons afflicted with carcinoma also have pseudopolyposis[24,62]. The incidence of carcinoma of the colon in ulcerative colitis is much greater than is to be found in the general population of comparable age (say 5% as against 0.011%)[5]. From the facts as presented it seems clear that carcinoma of the colon, of a type difficult to control and appearing under circumstances making it difficult to recognize early, constitutes a clear and present danger to patients with chronic ulcerative colitis not wholly restrained. Pseudopolyposis is evidence of severe destructive disease and of excessive regenerative efforts, and also masks the presence of adenomas which are true precancerous lesions[31]. This indication is therefore justified.

3. *Failure of Ileostomy to Control the Disease.* The disease may continue to manifest activity by one or more signs such as bloody rectal discharge, inability to regain weight, anemia, chronic skin infections, the appearance of arthritis or erythema nodosum, and thrombophlebitis. These may be considered evidences of intractability for which in reality ileostomy has been the first stage in surgical management. Exacerbations of acute disease may occur and one such is considered an indication for colectomy to prevent serious complications which may cost the life of the patient[55].

Indications for Proctectomy. Local sepsis, scarring, stricture, polyposis, and bloody discharge are all indications for removal of the rectal stump. Where none of these signs exist it may be preserved in the hope that it can later be used. If a specific treatment for ulcerative colitis should be found, a few patients can thus be given a functioning rectum.

Combined Operations. One-stage total colectomy and one-stage colectomy following a preliminary ileostomy have been successfully accomplished in the dire clinical states of massive hemorrhage, acute perforation of the colon, and acute fulminating disease. It is not surprising, then, to find combined operations used at a time of election. Ileostomy and partial colectomy have been performed together in conditions with indications for colectomy, with apparent satisfaction. The mortality and morbidity cannot yet be determined from the limited experi-

ence, though Miller *et al.*[56] reported 24 instances without fatality. Obvious advantages lie in the clean, free operative field offered the surgeon and in the decreased hospital time offered the patient. An important discovery has been that these patients recover more rapidly and more completely from the ravages of the disease than after ileostomy alone. The usefulness of the combined procedure of ileostomy and partial colectomy will be known when further experience makes apparent its limitations[4,12,22,25,49,56,57].

Vagotomy As a Method of Surgical Therapy. Mention must be made of an entirely different surgical approach to the problems of ulcerative colitis but one which is still considered to be in the experimental stage[29,30,32,70]. Dennis hoped to avoid the mutilation and the annoying complications of the orthodox surgical methods and has therefore employed vagotomy. The sum and substance of this experiment to date can be given in no better fashion than by quoting without comment the conclusions of Eddy[32]:

1. Within a maximum 3-year follow-up period, idiopathic ulcerative colitis and regional ileitis respond favorably in a majority of cases to division of the vagus nerves.

2. No patient should be subjected to vagotomy without critical evaluation of 4 factors which may be present; namely, massive hemorrhage, fibrosis and loss of colon distensibility, extensive ulceration, and long duration of the disease process.

3. Patients with disease existent for 5 years or more display a less favorable response to vagotomy than those cases with commensurably severe disease of lesser duration. Subjective and objective improvement may occur, and yet there continues in the colon an inflammatory reaction indistinguishable from carcinoma except by pathological examination. Such patients require colectomy.

4. The vagotomized colitis subject in whom previous gastroduodenal disease existed displays decreased gastric motility for a longer period, and shows a more consistent result with the Hollander insulin test than does the peptic ulcer patient treated by vagal section.

5. Vagotomy appears to benefit by decreasing intestinal motility and spasm. It also seems to interrupt a cycle of nervous and emotional imbalance which is affecting the colon, and acts as if the distribution of the vagus nerves extended to the distal colon and rectum.

6. If extended to an indiscriminate and unselected case series this treatment will in some instances provide disappointing results. In the face of a high carcinoma incidence in colitis patients, election of a treatment method aimed at salvage of the colon requires critical evaluation. For these reasons the procedure of vagotomy must still be considered in the investigative stage.

The Mortality in Surgery. There has been great encouragement to the surgeon in the marked lowering of mortality rates for operations in ulcerative colitis during the past few years. It is not the result of narrowed indications, as we have seen, but rather it reflects the vastly improved methods of medical and surgical care. It is important to realize that the mortality for ileostomy and colectomy is no longer "prohibitive" or out of the range of purely medical mortality. In 1932 Bargen, Brown, and Rankin[6] reported their mortality for ileostomy as 66% in the emergency group and 50% when done by election. In 1941, Cave and Thompson[23] gave corresponding figures as 50% and 9%. In 1950 Colcock[25] reported

from the Lahey Clinic that whereas the mortality from all ileostomies performed before 1947 was 18%, the rate for the following 2 years was 5.6%. It should be noted that the Lahey Clinic employs the widest range of indications of any group reporting, and that many of these fatalities are in reality chargeable to the disease. Brown, Gleckler, and Jones[12] reported an 8% mortality for 90 ileostomies. In the acutely toxic group it was 23% whereas in the nontoxic group there were no deaths in 43 operations. Ileostomy in ulcerative colitis should now carry a mortality rate in the neighborhood of 5%[36].

Colectomy is usually accomplished in 2 stages as a partial or subtotal colectomy and then proctosigmoidectomy. The entire colon has been removed in 1 stage successfully in the face of severe complicated disease but the true mortality rate must await further experience. Partial colectomy has carried a fatality rate from 6.7% to 15.8% including those performed as emergencies and without selection from the records of only the most recent years[12,19,55]. Proctosigmoidectomy in the same series has resulted in 2.7% to 4% operative deaths.

Late mortality following specific surgical procedures cannot be determined with any degree of accuracy from published reports. Three papers include follow-up studies of surgically treated cases for 12 years, 20 years, and 24 years[8,19,33]. The percentage of deaths among the survivors of operation ranged from 15% to 26%. Fully four-fifths of the patients in these studies were operated upon before 1940.

It may be helpful to indicate an expected patient mortality from the surgical treatment of ulcerative colitis which would include all of the operations performed. Brown, Gleckler, and Jones[12] gave the Cleveland Clinic experience as 14%. Dennis[27] reported his as 8% up to 1944. The Lahey group gave theirs as 22.3% for the years from 1927 to 1946. It is startling to note that in 1945 and 1946 some 75 patients were operated upon with a mortality of only 4%[19]. Dennis[30] further reports that from 1944 to 1946 surgery was performed on nearly all patients seen with ulcerative colitis with a hospital mortality below 10%. It is safe to assume, therefore, that the total patient surgical mortality now is less than 10%.

The Results of Surgical Management. Since operation is reserved for those whose disease has been uncontrolled otherwise, this becomes a highly selective group in which a fairly high mortality rate and a not too high rehabilitation rate could well be accepted. The mortality rate is seen to be low, not exceeding that to be expected under purely medical management of ulcerative colitis.

Ileostomy once performed in ulcerative colitis must be looked upon as permanent. It is very useful in ameliorating the severe symptoms and may, though rarely, bring about a lasting remission. The 2 most valuable studies on the ileostomy patient with respect to complications of the operation and the effect on the disease are those of Bargen *et al.*[8], and Brown, Gleckler, and Jones[12]. The complications pertaining to ileostomy alone are obstruction, prolapse, abscess, and fistula. Obstruction and prolapse may occur early in the postoperative period, or months and years later. The exact incidence to be expected cannot be ascertained. The more important discovery was that ileostomy alone could neither cure the disease nor prevent subsequent complications of an active colitis, including acute exacerbations of the disease. It is obvious, therefore, that colectomy must be anticipated in upwards of 80% of patients with an initial ileostomy. The longer the period of observation

after an initial ileostomy the greater the incidence of carcinoma that is found. Failure of ileostomy to cure the colitis and the real threat of carcinoma developing in the retained colon have caused Dennis[30] and Lahey[49] to advocate colectomy in all patients with ileostomy.

An ileostomy can rarely be closed. It has been tried on numerous occasions but with a minimum of success. Cattell and Sachs[19] present the experience that may be expected. Of 145 patients with ileostomy there was an attempted closure in 14 with 6 failures, and only 15 patients are being treated without removal of a part or all of the colon. It has been hoped that, by performing ileostomy earlier in the disease before irreversible changes in the colon have occurred, perhaps more might be closed. The known tendency for the disease to progress in the colon in spite of relief of symptoms by ileostomy precludes optimism. Lahey[49] tells of a series of 25 ileostomies performed in early cases on patients whose colons might have been expected to revert to normal and in whom the ileostomy was closed after the disease had become inactive. One-third experienced signs of renewed active disease. It has been shown beyond doubt that not more than 10% of ileostomy patients will meet the specifications that permit of attempt at closure, and from one-third to one-half of these will have renewed ulcerative colitis.

The degree of rehabilitation following surgical procedures is quite amazing to those who have looked upon the permanent ileostomy as a perpetual barrier to a normal existence. There are standards of measurement peculiar to each examiner that defy exact definition, yet are fully expressive. Cattell[18] states that 75% of their patients following total colectomy have resumed their former occupations. Ault[3] reports that all 17 of his patients available for follow-up have been rehabilitated, though he frankly states that as time passes this rate may not be sustained. From 104 patients who had had operations for ulcerative colitis McKittrick and Risley[55] obtained the information that 84% considered themselves in good health, and 97% were working as housewives, were in school, or were gainfully employed. Elsom and Ferguson[33] followed 20 patients in their surgical group for 1 to 12 years; 19 led a reasonably normal life; in 8 activities were not fully normal inasmuch as they had to take a lighter than usual occupation.

What of the Ileostomy Patient? The thought of permanent ileostomy has been one of repugnance, and as such has been a deterrent to the physician in the exercise of his honest clinical judgement when the need for surgery has been apparent. More or less invalidism has been regarded as preferable to the loathsome ileostomy. If it can be shown that surgical treatment will restore these patients to a healthful state but at the price of ileostomy, it is pertinent to determine the adjustment they can make to the social and economic problems presented to them. Nowhere is there a finer exposition of the triumphs and tribulations involved than in the conscientious, searching study made by McKittrick and Moore of 104 such patients[54].

The most important advance in the care of these patients has been the development in the last 6 years of water-tight, air-tight appliances that are inconspicuous, require minimum care, and can be worn with confidence. Indeed, the measure of control over ileal discharge is frequently greater than the disease had allowed before operation. The newer appliance permits all of the ordinary physical activities of work and recreation, includ-

ing swimming, and places no premium on travel. Hard physical labor has been found difficult to manage by some.

The extraordinary manner in which these dependent, morose, even belligerent individuals accept with gratitude the inconvenience of an ileostomy in exchange for good health and a chance to reenter social and economic competition is most gratifying. Courtship and satisfactory resolution of sexual problems in married couples have been successfully accomplished more often than they have failed. Pregnancies successfully carried through have been frequently reported, though obstetrical problems peculiar to ileostomy and the reconstructed pelvic floor after proctosigmoidectomy have not been fully explored.

The ileostomy patient free of his disease must be regarded as fully able to compete successfully in the social and economic life of his environment in spite of his inconvenience. With wise, sympathetic guidance from his surgeon and physician this goal can be achieved in nearly all surgically treated patients.

Summary. Chronic ulcerative colitis is primarily a disease requiring medical management, but subject to local and systemic complications that require surgical treatment in from 10% to 40% of patients seen. There is no known medical cure.

The mortality under good medical management should not exceed 10%. Patients are selected for surgical treatment by virtue of complications of the disease which may be acute or chronic in nature, requiring operations either to save life or to control or cure the disease by removal of the colon. The total surgical mortality in this selected group should not exceed 10%. The late mortality following each form of management appears to be greatly in favor of the surgically treated group.

Invalidism and disability, both social and economic, appear in 50% or more of those patients continued under good medical supervision. Patients treated by surgical means have shown a full rehabilitation rate of 70% to 95% despite the complications of the disease that led to surgery, the sacrifice of colon, and the inconvenience of a permanent ileostomy.

The indications for surgery are not subject to universal agreement. The vagaries of the disease, the variety of surgical and medical experience, the differences in definition of complications, phases of the disease, chronicity, and disability, together with a lack of understanding of the true nature of the disease, all combine to make agreement impossible. The indications that have been advocated for the selection of patients for operation have been discussed in the light of present knowledge and experience.

The modern surgical treatment of ulcerative colitis is about 20 years old and has utilized ileostomy, partial colectomy, and proctosigmoidectomy as standard, graded procedures. The tendency has been to follow ileostomy with colectomy in an ever increasing number of patients to cure the disease, to rehabilitate chronic invalids into productive citizens, and to prevent the development of carcinoma. It has been recently demonstrated that ileostomy may be safely combined with partial or total colectomy as a life saving measure and as a procedure of election. Vagotomy has been used for the control of the disease in a limited way and is to be considered as purely experimental at this time.

It has been abundantly proved that the patient with a permanent ileostomy can live happily and normally and can compete successfully in the economic and social life of his community. Though not a desirable accompani-

ment of cure, most of these patients consider the inconvenience of ileostomy as a fair trade for the relief obtained from the handicaps imposed by the disease. A great contribution to the contentment of the ileostomy patient has been the development of appliances that permit him to enter into his normal social and physical activities with the confidence that his ileostomy is completely and inoffensively controlled.

Surgery has become an important and indispensable part of the total management of chronic ulcerative colitis.

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OPHTHALMOLOGY

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OCULAR PHAKOMATOSES*

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THE term "phakomatoses" was proposed by Van der Hoeve[44] in 1923 to classify or describe the two disease processes known as tuberous sclerosis and neurofibromatosis. From the Greek word "phakos," meaning mother-spot or birthmark, the term implied the presence of cutaneous "spots" or tumefactions so often characteristic of these two diseases.

In 1932 Van der Hoeve[45] clarified his terminology further and extended the meaning of the term "phakomatoses" to include von Hippel-Lindau disease as well as tuberous sclerosis and neurofibromatosis. He suggested that the term "nevus" or "birthmark" should be used to designate spots in the skin which contain nevus cells, because true nevi are found only in the skin. He proposed the word "phakos" to describe a spot congenital in origin, and often hereditary, which could be found in different organs or tissues of the body. Thus, a phakos is a nevus (spot) without nevus cells, and a nevus is a phakos (spot) with nevus cells.

In 1937 Van der Hoeve, with Brouwer and Mahoney[8], clarified the term "phakomatosis" further and added Sturge-Weber syndrome to the group. They pointed out that 1) all these diseases are congenital or hereditary or both; 2) all may show phakoi, which are spots in the skin and other organs (such as the heterotopic spots in the brain of tuberous sclerosis and von Recklinghausen's disease); 3) all may show phakomata, which are tumefactions in different parts of the body, such as adenoma sebaceum of tuberous sclerosis and neurofibromas of von Recklinghausen's disease; and 4) all may show true or "real" blastomas which may be benign or malignant. Also, all 4 diseases are often accompanied by other congenital aberrations and very frequently mental disturbances such as backwardness, imbecility and idiocy, and epilepsy.

Therefore, there are now in this grouping 4 different disease processes, namely: 1) tuberous sclerosis (Bourneville's disease), 2) neurofibromatosis (von Recklinghausen's disease), 3) *angiomatosis retinae et cerebelli* (von Hippel-Lindau disease), and 4) nevus flammeus and glaucoma (Sturge-Weber syndrome).

* Abridgment and revision of thesis submitted by Dr. Kirby to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Ophthalmology.

Tuberous Sclerosis (Bourneville's Disease). Bourneville[6] in 1880 first recognized tuberous sclerosis as a pathologic entity. The condition is referred to by many as Bourneville's disease and by others as epiloia. In a series of papers between 1880 and 1898 Bourneville described the disease and named it "tuberous sclerosis" because of the "potato-like" appearance of the morbid foci. He noted the coexistence of the condition with adenoma sebaceum, but he considered it coincidental. As a result of the work of Vogt[46] in 1908 the more complete syndrome of mental deficiency, epilepsy, and adenoma sebaceum was established. Subsequent reports confirmed the earlier work of Bourneville and Vogt and also showed evidence that incomplete forms of the syndrome occur. The study by Critchley and Earl[14] in 1932 on tuberous sclerosis and allied conditions is one of the most comprehensive done in recent years.

In 1940 Reese[38] pointed out the histologic similarity between the ocular tumors of tuberous sclerosis and the hyaline excrescences that are sometimes present in the optic disks of otherwise normal patients. According to Reese, hyaline excrescences of the optic disk may be one of the clinical variants of tuberous sclerosis.

This interpretation has not been accepted generally. However, the fact that these hyaline bodies or drusen in the optic disks are not stationary congenital anomalies but may cause progressive defects in the visual fields is indicated by several recent reports as noted by Rucker[39].

The etiology of tuberous sclerosis is unknown but is probably hereditary. According to Koch and Walsh[26] in 1939, Yakovlev and Gutherie[50] considered the disease entity tuberous sclerosis to be a result of a developmental anomaly commencing early in fetal life and eventuating in widespread metaplasia which affects chiefly the ectodermal tissues but may also involve both mesodermal and entodermal derivatives.

Many writers have reported histories of the disease in which it affected more than one member of a family or in which some clinical variant, such as epilepsy or feeblemindedness, was present in other members of the family. Tuberous sclerosis in 3 children of the same family was reported by Miles and Dixon[33] in 1949. In each of these children, retinal lesions, radiopaque areas in the brain, abnormal encephalograms, and epileptiform seizures were present. The incomplete or variant forms of tuberous sclerosis, common in the family of a true case, may vary greatly. Individuals with the incomplete syndrome may remain useful members of society with a normal life span.

Tuberous sclerosis is characterized by 1) retarded mental development, 2) occurrence of epileptiform seizures, and 3) occurrence of tumors of one or more organs, usually the skin, brain, and eyes, often the liver, kidneys, and heart, and possibly the gastrointestinal tract. Variations from the typical may occur and only 1 component of the triad may be found.

Symptoms arise early in the true case of tuberous sclerosis, usually in infancy or early childhood. Physical or mental developmental delay is often the first symptom noted, the cutaneous lesions usually appearing during the first 10 years of life. The epilepsy associated with tuberous sclerosis may vary considerably in severity. The onset is usually in the first 2 years of life. Unlike many other forms of epilepsy, there may be long periods of remission, but the mental deterioration usually progresses steadily in spite of the remissions. Roentgenologically, accord-

ing to Camp[9], the combination of small irregular areas of calcification within the cerebral cortex and basal ganglia with patchy zones of hyperostosis in the diploë and internal table of the skull would seem to be characteristic of tuberous sclerosis.

Ocular Manifestations. Subjective ocular or visual symptoms are rarely associated with tuberous sclerosis. Usually the ocular manifestations are objective.

The most significant finding is retinal tumor. The clinical appearance of the retinal tumors of tuberous sclerosis was first described by Van der Hoeve. According to Duke-Elder[20], pathologic examinations have been made by Van der Hoeve in 1923, Schob[41] in 1925, Periz[36] in 1930, Kochenmeister[27] in 1935, and Messinger and Clarke[32] in 1937.

As seen with the ophthalmoscope, the retinal tumors may be of 2 classes, large nodular tumors which extend into the vitreous, and flat, oval, gray areas. Both eyes may be affected, and both types of lesions may be present in the same eye. The nodular tumors are more often near the disk than in other parts of the retina. They appear as a conglomerate mass of small glistening nodules and are often described as resembling a "white mulberry". The flat gray areas are more common than than the nodular tumors and are frequently multiple. They are more often noted away from the disk than near it.

According to Koch and Walsh[26] in 1939, the ratio of the cases with retinal tumors to the total number of cases is 1:5. Undoubtedly this ratio would be altered with more detailed study of the fundus in each case.

According to Van der Hoeve, the tumor originates in the nerve fiber layer. He expressed the belief that the typical cells were so-called glioneurocytes which had not become differentiated into glial cells or ganglion cells and that they were descendants of the first anlage of the retina.

The tissue sections in Messinger and Clarke's case were studied by Ida Mann, in whose opinion the cells were glial in origin, probably being derived from the glial cells of the inner neuroblastic layer during the second stage of retinal differentiation, which takes place from the 6th week to the 3rd month of intrauterine development. According to Messinger and Clarke, the cytologic evidence, together with the embryologic possibilities, justifies the conclusion that these tumors are essentially gliomatous.

Neurofibromatosis (von Recklinghausen's Disease). Neurofibromatosis is a congenital disease which affects the nervous system, the skin, and other organs. It is characterized by multiple tumors of the cranial, spinal, peripheral, and sympathetic nerves. Tumors, nevi, and pigmented *café au lait* spots affect the skin. Defective development of the central nervous system, anomalies of bone, buphthalmos, and other developmental anomalies are sometimes noted. Incomplete forms of the disease are often observed.

Ocular Manifestations. The eyelids may be involved by isolated fibromas or by plexiform neurofibromatosis. The plexiform involvement of the superficial nerves of the lids may be quite extensive and elephantiasis of the lids may result. The skin of the affected lids often has a brawny and bronzed appearance. Neurofibromatosis also may involve the conjunctiva, and several cases of neurofibromatosis of the iris have been reported.

Neurofibromatosis of the choroid and ciliary body is known to occur. It may be localized to minute areas arising probably from the ciliary nerves, or it may originate in the perivascular nerve plexus and involve the entire choroid

and ciliary body. The condition may be symptomless and found only on routine necropsy, or it may be associated with glaucoma.

The orbit may be involved either by a solitary neurofibroma or by plexiform neurofibromatosis. Proptosis is common and may be extreme, and limitation of movement and displacement of the globe are frequent. The bony orbit is sometimes enlarged and deformed owing to orbital neurofibromatosis.

Pulsating exophthalmos is occasionally reported in neurofibromatosis. The pulsation is not expansile and there is no bruit. The absence of these two findings differentiates neurofibromatosis of the orbit from carotid-cavernous fistula. The best explanation for the pulsation is that it is probably due to the pulsation of the brain transmitted to the orbit through defects of the bones of the orbit. These defects may be congenital, or they may be the result of erosion by the tumor mass of neurofibromatosis.

Congenital glaucoma (buphthalmos) associated with neurofibromatosis may be present at birth, and there is usually neurofibromatous involvement of the skin about the eye and face in these cases. The exact cause of the glaucoma in these cases is not known. Congenital defects of the filtration angle, involvement of the ciliary nerves, and anterior displacement of the iris root have been mentioned as possible factors in the development of glaucoma.

Retinal and Optic Nerve Tumors of Neurofibromatosis. The clinical appearances of retinal and optic disk tumors of neurofibromatosis are difficult and often impossible to distinguish from those of tuberous sclerosis. The similarity of the ocular affections of these 2 diseases was one of the reasons why Van der Hoeve in 1923 brought them into the same group, "phakomatoses".

In 1932 Van der Hoeve described the optic nerve and retinal tumors found in a patient with neurofibromatosis. One eye showed a large cyst at the disk with glial proliferation. The other eye showed 2 retinal lesions which microscopically exhibited the same cells and fibers described in tuberous sclerosis. However, one of the lesions contained an area of large vessels which were more like those of the tumors of von Hippel's disease. At that time Van der Hoeve observed that the retinal affections of von Recklinghausen's disease seemed to stand somewhere between those of tuberous sclerosis and von Hippel's disease.

A comprehensive clinical and pathologic study of the optic nerve tumors in neurofibromatosis was reported by Davis[18] in 1940. He concluded that the so-called primary tumors of the optic nerve appear as gliomas or endotheliomas, the former being the more common. The endotheliomas arise from the dural or arachnoid sheaths of the nerve and resemble those found in the brain known as "meningiomas" or "meningeal fibroblastomas". Some of the tumors exhibit both gliomatous and endotheliomatous features, producing a complex histologic picture. In Davis' opinion the tumors of the optic nerve are characteristically true tumors that should be designated as gliomas. The predominant cell types are astrocytes, and the tumors should be designated as astrocytomas. Dresner and Montgomery[19] in 1949 reviewed the literature of primary optic atrophy associated with neurofibromatosis. Their review found that 85% of the cases involved gliomas of the optic nerve or chiasm.

The tumors of the optic nerve and the neurofibromas of the peripheral nerves seem to be expressions of the same general diseases, but they are histologically different. The tumor of

the optic nerve is not a neurofibroma; it is usually a glioma or at times an endothelioma.

Pathology. Neuropathologists usually describe 2 types of neurofibromas: 1) solitary: the axis cylinders of the nerve bundle from which the tumor arose are in the capsule and not within the tumor substance, and the tumor is referred to as a perineural fibroblastoma; 2) multiple: these tumors are associated with other stigmas of von Recklinghausen's disease. The axis cylinders of the nerve bundle course through the substance of the tumor; thus it is a true neurofibroma.

There are 2 schools of thought on the origin of the tumors of neurofibromatosis: Some believe that the tumor arises from the cells of the sheath of Schwann and that the cells are neuroectodermal in origin. Others assert that they arise from the fibrous elements of the nerve and that the fibroblast is the type cell of the tumor.

Kernohan and Parker[25] in 1932 reported the postmortem findings in a case of von Recklinghausen's disease, the clinical findings of which had been reported earlier by Parker[35] in 1922. The tumor of the optic nerve was a typical dural endothelioma. The tumors of the cranial nerves other than the optic, and the tumors of the dorsal roots of the spinal nerves, were of 2 types, neurofibromas and perineural fibroblastomas. There were gliomas of the spinal cord and intracranial meningiomas, and there was syringomyelia of the cord. The gliomas belonged to the astrocytoma and cellular ependymoma types. The meningiomas showed all stages of activity, from those of the psammoma type to those which simulated fibrosarcoma of low-grade malignancy.

So-called Mixed Tuberous Sclerosis and Neurofibromatosis. The difficulties encountered at times, even after histologic studies, in the differential diagnosis of the ocular manifestations of tuberous sclerosis and neurofibromatosis are illustrated by the case of tumor of the optic disk reported by White and Loewenstein[49]. These authors concluded that the growth was a "phakoma arising from the neuroectodermal cells of the optic stalk" but that it could not be classified definitely as to type.

Two cases of so-called mixed tuberous sclerosis and neurofibromatosis observed at the Mayo Clinic merit description. In one, the provisional diagnosis of both neurofibromatosis and tuberous sclerosis was made. In the other a tentative diagnosis of tuberous sclerosis was made, but neurofibromatosis could not be ruled out. These cases are presented to illustrate the difficulties which might be encountered in making a clinical diagnosis.

Case 1. A white man, aged 24 years, was admitted to the clinic. His family history was negative. He was the 4th of 9 children, and all the others were living and well. His mental and physical progress as a child had been slow.

Examination revealed a right convergent strabismus which had been present since childhood. There was mild weakness of the right lateral rectus muscle, and the right eye was amblyopic. The results of funduscopic examination were negative. The vision was 6/30 on the right and 6/6 on the left. There were adenomata sebaceum of the face and neck, *café au lait* spots of the trunk, and many subcutaneous nodules of the trunk and extremities, some of which definitely followed the nerve trunks. Areas of macular atrophy also were present. General examination revealed a congenital right inguinal hernia with an undescended right testicle. There was a congenital anomaly of the right forearm and wrist with fusion of the radial and carpal bones and an anomaly of the lower end of the ulna. There was megalodactyly of the right middle finger, the enlargement being due mostly to hypertrophy of soft tissue. The patient had no neurologic symptoms. A roentgenogram of the head was negative.

The provisional diagnosis was neurofibromatosis and tuberous sclerosis with mental deficiency and congenital anomalies.

CASE 2. A white man, aged 30 years, was admitted to the clinic. He was an only child. His father and mother were living and well, but his father had cutaneous tags on the body. One week before admission during a routine examination, the patient's local oculist had noted a tumor mass of the left optic disk. The same oculist had examined him 6 months previously, at which time the tumor mass had not been present. The vision was 6/60 and 14/56 in the right eye, 6/6 and 14/14 in the left. There was a limited opacity in the upper nasal quadrant of the right lens which was known to have been present for many years. In the left eye there was an oval mass extending off the upper temporal edge of the optic disk, concealing the vessels but apparently lying on top of or in the retina. The lesion resembled a conglomerate mass of hyaline bodies and suggested some form of phakomatosis, either tuberous sclerosis or neurofibromatosis.

There were no neurologic symptoms and the patient was of normal intelligence. He assumed a normal status in business and in his community.

Dermatologic consultation revealed small red spots of the nose and face which had been present since early childhood. The patient stated that roentgen therapy and "acid" treatments had not improved the lesions. The latter were not typical but suggested adenoma sebaceum. The patient had a few pigmented nevi, one vitiliginous area and several fibrous cutaneous tags of the shoulders. There were no *café au lait* spots. To the dermatologist the cutaneous picture resembled neurofibromatosis more than it did tuberous sclerosis.

The results of general examination were negative except for a large hard tumor mass of the inner aspect of the right upper arm. The mass had been present for many years with no noticeable change. A roentgenogram revealed that the mass was a broad-based osteochondroma arising from the medial posterior aspect of the upper half of the right humerus.

A roentgenogram of the head was not obtained.

The appearance of the retinal tumor, which so closely resembled those classically described in tuberous sclerosis, plus the atypical lesions of the face, prompted a tentative diagnosis of tuberous sclerosis by the ophthalmologist. Neurofibromatosis could not be ruled out, especially in view of the other cutaneous findings.

Angiomatosis and Arteriovenous Communications in the Retina. The history of von Hippel-Lindau disease is extensive. According to Cushing and Bailey in 1928[15], the first example in the literature was a clinical record by Fuchs[22] in 1882. Fuchs interpreted the ophthalmoscopic picture as an arteriovenous aneurysm. The true nature of the disease was first recognized in 1894 by Collins[11], who concluded from a pathologic study that the lesion was a "capillary nevus which in places had undergone cystic degeneration".

In 1904 von Hippel[24] reported 2 cases which he had observed over a period of several years, and later he was able to gain a pathologic study of one of the eyes. He designated the disease as "angiomatosis retinae".

In 1908 Coats[10] described 6 cases of retinal disease with massive exudation and included examples collected from the literature in which the primary lesion seemed to be an arteriovenous communication.

During the subsequent few years there was some confusion concerning the true pathogenesis of these lesions. The gliosis which often accompanies the long-standing lesions was considered by some writers as the primary process and vascularity as a reactive incident. However, the work of Brandt[7] in 1921 and Berblinger[2] in 1922 definitely established the true pathologic character of the primary lesion. Brandt emphasized that the lesion was a true tumor and differed from the congenital angiomas in other parts of the body in that it did not begin to show clinical evidence of its presence until the second or third decade of life.

Postmortem examination in some of the earlier cases revealed that other organs were sometimes involved by similar angiomatous lesions. It re-

mained for Lindau[30,31] in 1926 and 1927 to establish the true relationship between the retinal lesions and cerebellar tumors and cysts of the kidneys, epididymis, pancreas, and adrenals. Lindau also suggested that the disease resembles and probably belongs to the same group as tuberous sclerosis. It was in 1932 that Van der Hoeve[45] extended the term "phakomatoses" to include von Hippel-Lindau disease along with tuberous sclerosis and neurofibromatosis.

Since Lindau's publications of 1926 and 1927, other workers have added to the knowledge of the disease. Among these are the comprehensive review and classification of vascular anomalies by Cushing and Bailey[15] and the work of Dandy[16,17] in 1928. The clinical and pathologic findings in 4 cases of this disease were reported by Craig, Wagener and Kernohan[13] in 1941. Rados[37] in 1950 reported 2 cases and presented an extensive review of the history and literature of von Hippel-Lindau disease.

General Considerations. There are many cases of von Hippel-Lindau disease in which the syndrome is incomplete. Von Hippel's disease (angiomatosis retinae) often occurs without any involvement of other structures. Most authors use the term "Lindau's disease" to include the more complete syndrome of retinal, cerebellar, and possibly other involvements. However, it is known that angiomatous tumors do occur in the cerebellum and elsewhere without any evidence of retinal affection. Lindau found that 20% of the patients with angiomatosis retinae also had or developed intracranial complications, which were cysts or angioblastic tumors of the cerebellum or the medulla. Dandy did not find such a high incidence. In all of the 4 cases studied by Craig, Wagener, and Kernohan there was retinal as well as cerebellar involvement.

Embryologically, the disease was considered by Lindau to be due to a disorder in the mesoderm during the third embryonic month. Also, he concluded that the matrix for the development of angioma formation in the cerebellum appeared to be the vascular mesenchymal surface of the covering of the 4th ventricle. In his paper on the natural history of retinal neoplasms, Collins[12] in 1928 stated that the blood vessels of the retina are its only mesoblastic constituent and may be the seat of origin of capillary angiomas and possibly angiosarcomas.

Angiomatosis Retinae. The classic ophthalmoscopic picture of angiomatosis retinae consists of a pair of enlarged tortuous vessels extending from the disk into a tumor mass, situated usually in the peripheral part of the retina. The vessels may be of practically the same color owing to arteriovenous communication, but the vein is usually the larger of the two and the arteriole may be "beaded." More than 1 pair of vessels may be involved and the other small tumor masses may be present.

The disease is progressive and secondary exudative and degenerative changes gradually develop. About the tumor mass, edema, hemorrhages, and grayish white exudates may be seen. Similar exudates may occur along the affected vessels and in other parts of the retina, especially in the macular region. Subretinal edema with detachment of the retina, complicated cataract, and secondary glaucoma may develop in the advanced stages of the disease process. In some cases gliosis of the retina may be extensive and may confuse the clinical interpretation of the ophthalmoscopic picture, since it may conceal the underlying primary vascular lesion.

The generally accepted concept of the nature of the process in typical cases of angiomatosis retinae is that the tumor mass is congenital and that the progressive exudative and degenerative changes in the retina result from the gradual enlargement of the tumor and the consequent increasing interference with the retinal circulation. However, in some cases diagnosed clinically as von Hippel's disease, hugely dilated companion vessels are seen which seem to communicate with each other without passing through a definite tumor mass. In such cases, secondary degenerative changes may fail to develop during an extended period of observation. Other cases are encountered in which there is diffuse dilatation of all the retinal vessels with edema and exudates in the retina but without a definite visible tumor mass. Therefore some observers contend that the lesions of von Hippel's disease are not always due to the increase in size of a congenitally present angioma. Early changes in the vessels, such as diffuse dilatation, "beading" of the arterioles, and changes suggestive of arteritis and phlebitis, may be encountered several years before a definite tumor mass or an arteriovenous communication can be demonstrated. This suggests that the development of the angioma may be a late rather than an early feature of the disease. However, it seems obvious that the underlying cause must be some congenital defect of the vessels themselves. It is possible that, if the diagnosis of angiomatosis retinae (von Hippel's disease) were reserved for those cases with a definite primary angioblastoma of the retina, the percentage showing or developing the complete syndrome of Lindau disease would be much higher.

Ophthalmoscopically, the disease must be differentiated from several conditions: 1) *Multiple congenital aneurysms.* If companion vessels are not affected, the disease is probably not angiomatosis retinae. 2) *Glioma of the retina*, in instances in which extensive secondary gliosis has developed. 3) *Coats's disease* (external exudative or hemorrhagic retinitis with massive exudation into and under the retina). The late stages of this disease and of angiomatosis retinae may be practically identical in ophthalmoscopic appearances, and differential diagnosis may be impossible. Particularly in the presence of detachment of the retina or secondary glaucoma or both, the presence or absence of an angiomatous mass may be impossible to determine clinically. But, according to Rados, the early pictures of the two diseases are quite dissimilar. Vascular lesions with thromboses of small arteries and veins are a part of the pathologic changes of external exudative retinitis; but angioma formation occurs only in angiomatosis retinae. 4) *Congenital arteriovenous aneurysm.* In these cases, both arterioles and veins may be enlarged and tortuous but the scarcity or absence of secondary changes should differentiate them from angiomatosis retinae. According to Rados[37], "the angiomas, either tumors in the strict sense or vascular malformations, represent a separate group among the diseases of the retina, and the terms angioma and angiomatosis of the retina (hemangiomablastoma of von Hippel and Lindau) should not be used interchangeably."

Histologically, the retinal tumor is described as a hemangioblastoma, being composed of many immature vascular spaces and dependent on a congenital defect of the vascular development during the third month of fetal life. The vascular spaces are lined with endothelial cells, and the lumen may be so small that the cells appear in a cluster. Others may be quite dilated.

The vascular spaces are enmeshed in a connective tissue matrix which may contain glial cells and more endothelial cells. The tumor often exudes plasma and has a definite tendency to cyst formation. Newly formed vessels may be present as a result of the hemorrhages. Almost all hemangioblastomas have endothelial cells both within and between the blood spaces. Some of these cells are frequently laden with fat. The origin of the xanthic cells is not clear. Craig, Wagener, and Kernohan[13] suggested the possibility that the fat-laden cells may be an obstruction to the circulation of the blood and thus result in transudation which accumulates around the neoplasm and forms a cyst. Case 4 in their series showed a tumor in the right eye which did not contain xanthic cells and the retina was not detached. In the left eye was an angioma in which the intervascular and intravascular endothelial cells were laden with fat and there was total detachment of the retina. However, in the 2 cases reported by Rados, pseudoxanthoma cells were not present in the tumors and yet the retinas were detached. Further observations are needed to establish a possible relation between the presence or absence of xanthic cells and cyst formation or detachment of the retina.

The choice of treatment rests between roentgen irradiation, radium therapy, and diathermy to the affected eye. Radium therapy in early involvement may give better results than roentgen irradiation. Diathermy to the scleral surface and puncture of the underlying angioma have given good results in some cases. In 1947 Lewis[29] reviewed the cases in which angiomatosis retinae had been treated with diathermy and reported 2 cases of his own in which this treatment was successful. Vail[43] in 1949 reported another case with successful treatment. In Vail's opinion surface and puncture diathermy treatment is more efficient than roentgen or radium therapy.

Diagnosis. The diagnosis of Lindau disease can be made on the demonstration of a retinal angioma and cerebellar signs or symptoms. A familial history of the disease or its incomplete forms can be particularly helpful to the neurosurgeon in making a preoperative diagnosis.

Rados stated that, in Lindau disease, inheritance is of a "pleiotropic monogenic dominant variety affecting the tissues of mesodermal origin" and may occur in horizontal, vertical, horizontal-vertical, and collateral fashion. Members of families may have lesions in the eyes, in the central nervous system, or in both simultaneously.

Histologically, the cerebellar tumor is described as a hemangioblastoma and is composed of many immature vascular spaces lined with endothelial cells, the spaces may be small or greatly dilated, and endothelial cells may be present in the intervascular reticulum. The tumor is usually small, localized, and situated near the cortex or subcortical region. It is frequently seen as a small nodule in the wall of a large cyst. Those arising near the midline may project into the fourth ventricle. The cyst wall consists of glial cells and has no lining membrane. The primary involvement may be of the medulla or spinal cord and if so, the cystic regions may closely simulate or be associated with syringomyelia. The multiple vascular spaces usually have fat-laden endothelial cells both within and between the spaces. Involvement of the cerebrum is rare but does occur occasionally, as in the case reported by Rochat (quoted by Rados[37]).

The associated affections of other organs, such as the pancreas and liver, are usually simple cysts; however, hypernephroma of the kidneys is sometimes reported.

Nevus Flammeus and Glaucoma (Sturge-Weber Syndrome). Other names suggested for this disease include encephalotrigeminal angiomatosis, vascular encephalotrigeminal syndrome, neurocutaneous syndrome, meningocutaneous syndrome, Weber-Dimitri disease, congenital neuroectodermal dysplasia, Sturge-Kalischer disease, cutaneocerebral angioma, Sturge's disease, Krabbe's disease, and Brushfield-Wyatt syndrome. However, the term "Sturge-Weber syndrome" or "Sturge-Weber disease" is in most common usage.

According to O'Brien and Porter[34] in 1933, Schirmer[40] in 1860 was the first to record the association of vascular nevi of the face and glaucoma.

In 1879 Sturge[42] recorded a case with a "port wine" mark which involved the right side of the face, scalp, mouth, and pharynx. The right eye was enlarged, the retinal vessels were tortuous, and a purplish patch was seen in the fundus. Convulsive seizures of the opposite side of the body were attributed to a similar nevoid condition of the brain.

In 1922 and 1929 Weber[47,48] described the roentgenographic findings of Sturge-Weber syndrome. Elwyn[21] stated that Bergstrand, Olivecrona and Tönnis[3] in 1936 were the first to give the name "Sturge-Weber" to the disease. In the United States O'Brien and Porter[34] gave a comprehensive review and study of the literature in 1933. Since then other cases have been reported, and others can be found that are reported as angiomas of the choroid rather than by the name of the syndrome.

The syndrome is characterized by 1) vascular nevus of the face, 2) angiomatous involvement of the meninges and brain, 3) epilepsy, usually jacksonian and contralateral, 4) areas of intracranial calcification, and 5) unilateral buphthalmos in many cases.

Weber has interpreted the roentgenographic findings as calcareous deposits in the vessels of a meningeal angioma. Krabbe[28] in 1934 described the postmortem findings in a case and showed the calcification to be in the second and third layers of the cortex and not in the pia mater. The calvarium overlying the affected hemisphere is often thickened and asymmetric, and the hemisphere itself shows poor development or atrophy. Camp[9] stated that, in the Sturge-Weber syndrome, roentgenograms of the head reveal tortuous shadows of calcification corresponding to the shape of the convolutions of the atrophic cerebral cortex. The vascular markings of the diploë and internal table are not increased over the involved area. Similar calcification may be seen in cases of mental retardation without facial angiomas.

Ocular Manifestations. The most important ocular manifestation of the syndrome is glaucoma, which is usually on the side of the facial nevus. The vascular nevus and glaucoma may occur bilaterally as reported by Bock[5] in 1950. Glaucomatous cupping and atrophy of the optic disk are often noted.

Heterochromia of the iris and angioma of the choroid are frequently reported. Occasionally the latter is demonstrated clinically, but usually it is discovered by the pathologist after enucleation or at necropsy.

There is often no retinal change. Tortuosity of the arterioles and veins is sometimes noted. Reduction in caliber of the vessels, associated with glaucomatous cupping of the disk, has been observed. Sheathing of the retinal vessels and gliosis in the macular area also have been noted. Brouwer, Van der Hoeve, and Mahoney[8] in 1937 reported 1 case in which a large glioma of the retina was associated with the syndrome.

Changes in the visual field are usually those of glaucoma, but several cases

with homonymous hemianopsia have been reported.

Bielawski and Tatelman[4] reported a case with unilateral vascular nevus of the right side of the face, contralateral hemiparesis, mental deficiency, bilateral congenital glaucoma, and, in roentgenograms of the head, characteristic calcification outlining the convolutions of the cortex of the right occipital and parietal lobes with associated cortical atrophy. They used the term "neurocutaneous syndromes" instead of "phakomatoses" and stated that though intracranial calcification might occur in any of the four syndromes, "calcification conforming to the cerebral convolutional pattern is typical of encephalotrigeminal angiomatosis" (Sturge-Weber). They stated further that calcification typical of angiomas of the meninges might be seen in cases with or without the Sturge-Weber syndrome.

Green, Foster, and Berens[23] reported a case typical of the Sturge-Weber syndrome except for the absence of glaucoma. There were present a "port-wine mark" of the skin over the distribution of the first division of the right trigeminal nerve, generalized convulsions, left homonymous hemianopsia, roentgenologic evidence of calcification outlining the convolutions of the right occipital lobe, and electroencephalographic evidence of an epileptogenic focus in the right occipital lobe. A right occipital lobectomy was performed. Angiomatous malformations were present in the leptomeninges, and calcification was present in the second and third layers of the cerebral cortex. Eighteen months later, the hemianopsia was still present but no further convulsive seizures had occurred.

The glaucoma associated with Sturge-Weber syndrome is more often of the congenital or infantile type, but it may have its onset later in life and follow the course of chronic simple glaucoma. Anderson[1] in 1939 made the statement that apparently the glaucoma is associated with a facial nevus only when the nevus affects the lids or the conjunctiva. O'Brien and Porter stated that glaucoma is to be expected in cases of facial nevus which involve the lids, conjunctiva, episclera, iris, choroid, or other ocular structures. Bilateral glaucoma is probably more likely to occur in cases with nevi involving both sides of the face, but it has been reported in the presence of unilateral nevus. Angioma of the choroid is believed by most authors to be the basic or responsible factor in the development of glaucoma.

The exact mechanism of the production of the glaucoma is not known, but various hypotheses have been proposed. In his monograph on congenital glaucoma, Anderson in 1939 discussed these different hypotheses. He concluded that the association of nevus flammeus and glaucoma is due to some ill-understood influence acting in very early embryonic life. He stated that in some cases the actual cause of the glaucoma may be the presence of anomalies that occur in buphthalmos in general. The possibilities would be persistence of the uveal meshwork, the complete or partial obliteration of Schlemm's canal, or a posterior position of Schlemm's canal and the scleral spur. He stated further that the glaucoma may be due to the uveal angiomatous changes producing an increase in the intraocular fluid which is too much for normal channels of escape, or for those channels that are defective from sclerosis, adhesions, or angiomatous changes.

Relationship Between von Hippel-Lindau Disease and Stupge-Weber Syndrome. It is of particular interest to note some observations made by Anderson on the relationship and contrasts between von Hippel-Lindau disease and the Sturge-Weber syndrome. Anderson stated that the angiomas of the Sturge-Weber syndrome

TABLE 1.—SUMMARY OF FINDINGS IN CASES OF PHAKOMATOSES COLLECTED FROM FILES OF THE MAYO CLINIC

	Tuberous sclerosis (Bourneville)	*Neurofibromatosis (von Recklinghausen)**	*Angiomatosis*		*Nevus flammeus and glaucoma (Sturge-Weber)*
			von Hippel	*Lindau*	
NUMBER OF CASES	11	20	8	2	10
OCULAR LESIONS	7	20	8	2	7
Tumors					
Eyelids alone		5			
Orbit		3			
Eyelids and orbit		4			
Conjunctiva		3			
Optic nerve		4			
Astrocytoma (proved)		1			
Chiasm		2			
Retina					
Hyaline type	3				
Plaque type	3	1			
Angioma			6	2	
Arteriovenous aneurysm			2		
Choked disks		2		1	
Optic atrophy	1	6			
Buphthalmos					2
Chronic glaucoma					4
Hemianopsia					
Homonymous					1
Bitemporal		1			
Ocular palsies		1			
NEUROLOGIC LESIONS	11	9		2	10
Grand mal	9				8
Petit mal	4				
Mental retardation	7	4			4
Cerebellar		1		1	
Brain stem				1	
Spinal cord				1	
Hemiparesis					4
Nerve deafness		3			
Facial palsy		2			
CUTANEOUS LESIONS	10	17	1		10
Adenoma sebaceum	10				
Café au lait spots		10			
Subcutaneous nodules	4	7			
Nevoid tumors	3	2			
Lipomas			1		
Angiomas		1			10
ROENTGENOGRAMS OF HEAD	10	11	6	2	7
Calcification	7	1	1		4
Cortex	3				4
Basal ganglia	3				
Suprasellar	1	1			
Cerebellum	1				
Orbit			1		
Unlocalized	1				
Erosion					
Sella	1	1	1		
Orbital walls		2			
Acoustic meatus		1			

* Cases of neurofibromatosis without ocular findings were not used in this study.

are not true neoplasms, whereas the lesions of Lindau disease are true hemangioblastomas. The angiomas are more frequent in the cerebrum than in the cerebellum, but the true neoplasms are probably confined, or almost so, to the cerebellum. The retina and optic nerve are actually extensions of the central nervous system. The central nervous system has 2 separate systems of blood supply (cerebral and meningeal arteries), and the retina also has 2 supplies (central retinal artery and the choroidal network). Thus, the choroid appears as the "meninges" of the retina. This would somewhat explain the 2 separate entities, angiomatosis of the meninges (Sturge-Weber) and angiomatosis of the internal blood system (*angiomatosis retinae et cerebelli*).

The embryologic development of the vascular system would also support these observations. In the 2nd period of development the primordial plexus slowly begins to differentiate into arteries and veins. Any interference

during this stage might lead to true vascular tumor formation such as the hemangioblastomas of Lindau disease. Also, during this stage the posterior fossa and retina have a rich capillary network but no arteries or veins. This could possibly explain the frequency of vascular tumors of the cerebellum and occasional tumors of the retina. In the third period of development the dura and cranium are developing and the vascular system splits into a superficial, a dural, and a pial circulation. A maldevelopment of a vascular area during this period might result in a vascular nevus of the scalp, varices of the dura, or varices of the pia, or all 3 simultaneously.

Statistical Summary. The similarities and dissimilarities which exist between the ocular, neurologic, dermatologic, and cranial roentgenologic lesions in the 4 phakomatoses are illustrated by a series of cases taken from the files of the Mayo Clinic during the years 1940 through 1947. The findings in this series of cases are given in brief in Table 1.

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BOOK REVIEWS AND NOTICES

FUNDAMENTALS OF CLINICAL FLUOROSCOPY. By CHARLES B. STORCH, M.D., Adjunct, Radiodiagnostic Dept. and Radiotherapy Dept., Beth-El Hosp., Brooklyn, New York. Pp. 196; 217 ills. New York: Grune & Stratton, 1951. $6.75.

THIS new book is unique in current radiologic literature in that its purpose is to present only the methods and findings of the fluoroscopic technique; the roentgenographic findings are discussed briefly and in supplementary fashion. The study of the chest, esophagus, stomach, and colon is amply covered. Most of the important procedures and the helpful "tricks" of technique are mentioned and there are many useful illustrative diagrams indicating both methods and findings.

Dr. Storch does well to emphasize that fluoroscopy will usually be only the beginning of a satisfactory Roentgen examination. It seems to the Reviewer that he may not have stressed strongly enough that apparently negative examinations of the chest by fluoroscopy alone are all too often misleading and hazardous for the patient. It is fortunate that a sound and conservative guide is now available for students and for the many without any special roentgenologic training who employ fluoroscopy in their practice.

H. S.

THE TRANSMISSION OF NERVE IMPULSES AT NEUROEFFECTOR JUNCTIONS AND PERIPHERAL SYNAPSES. By ARTURO ROSENBLUETH, Chief, Dept. of Physiology and Pharmacol., Instituto Nacional de Cardiologia de Mexico. Pp. 328; 98 ills. New York: John Wiley & Sons, 1950. Price, $6.00.

THIS authoritative monograph will concern primarily the neurophysiologist and the theoretical pharmacologist. However, the logical and exhaustive analysis of all published data on this controversial subject, including the author's own critical experiments, has fascination for anyone interested in scientific argument. Electrical activity is important for nerve conduction and is the sign of depolarization which allows the release of acetylcholine at a synapse in sufficient concentration for stimulation. The electrical spike itself has an ineffectual amplitude and duration to accomplish this.

Synaptic delays and curare effects are examples of phenomena explained by accompanying chemical rather than electrical changes. Thus the doctrine of chemical transmission of nerve impulses in the case of synapses, both within autonomic ganglia and at somatic neuromuscular junctions, is convincingly established. The author argues that a chemical theory is quite as essential here as it was to explain the opposite physiological effects of identical electrical activity in adrenergic and cholinergic autonomic nerve fibers.

F. N.

JOHN HUNTER. By S. ROODHOUSE GLOYNE, M.D. Pp. 104; 16 ills. Baltimore: Williams & Wilkins, 1950. Price, $3.50.

THE author "has tried to tell the story of John Hunter in the setting of his period", a modest goal which no one could say he had failed to reach. But, it is not clear to the Reviewer why another life of this famous man was desirable, or what of significance Dr. Gloyne has added to the oft painted picture. He acknowledges his debt to a long line of witnesses, too numerous to mention. Under these circumstances a new book—or shall we say booklet?—on Hunter must have some very special offering in order to deserve shelf room; this we have failed to find. The text, except for frequent quotations from Hunter, is mediocre and not always accurate. One could hardly maintain, for instance, that Sir Thomas Browne, born 1605, "wrote a generation before Hunter", born 1728.

The 16 illustrations are good, but none are original and a good half are old friends that one often meets elsewhere. The book, "made and printed" in Edinburgh, is better printed than bound; in one copy at least the spine has already begun to break.

E. K.

WHEELER AND JACK'S HANDBOOK OF MEDICINE. Revised by ROBERT COOPE, M.S., B.Sc., F.R.C.P. 11th ed. Pp. 648; 62 ills. Baltimore: Williams & Wilkins, 1950. Price, $5.00.

TEN years have elapsed since the last edition of this handbook. Much has been rewritten, but it is unfortunate that the book has not been brought up to date. The emphasis, for example, is still upon the anatomic rather than the etiologic classification of the pneumonias, and one searches in vain for a

discussion of primary atypical or viroid pneumonia. Apparently penicillin is to be used in pneumococcic pneumonia only when sulfones have failed. No mention is made of the potential dangers of sulfone medication, nor does one find the sulfones mentioned under agranulocytosis.

The important lower nephron nephrosis syndrome is not included, nor is there any mention of disseminated lupus erythematosus. The treatment advised for pernicious anemia is very much out of date. None of the newer antibiotics (aureomycin, etc.) is included, and streptomycin and PAS are not mentioned under the treatment of any form of tuberculosis. The allergic diseases are very poorly handled despite their great frequency in practice.

It is possible, of course, that the intent to provide a concise handbook has necessitated these omissions, but it is the Reviewer's opinion that a book which attempts to cover so much with so little has no place in the Medicine of today. T. D.

History of the New England Female Medical College. By Frederick C. Waite. Pp. 132. Boston: Boston University School of Medicine, 1950. Price, $3.00.

The author, a fruitfully persistent delver in early American medical institutions, brings us this account of the first institution in the U.S. to teach medicine to women. Like the Woman's Medical College of Pennsylvania, its younger sister by 2 years, it was conceived (1848) in one of the liberal centers of this country during a period of considerable social ferment and new ideas. But whereas the Boston school found it desirable for financial reasons to merge with the Boston University's newly founded School of Medicine, the Philadelphia institution still flourishes. It surprised the Reviewer to read that proposals for accepting the school as a separate department of Harvard University to educate female physicians had been favorably received by its Corporation and Overseers. However, the disastrous Boston fire of November 1872 put an end to any thoughts of raising the necessary funds. At this point, Boston University, which was about to found a homeopathic medical college, also included the Female College, agreeing to pay its accumulated debts. In spite of asserted agreements to the contrary, according to the author, the name and identity of the latter were soon lost, leaving but one medical school in this country for teaching only women. This and more he details in his story, together with considerable background and sidelights that lift the product well above a bit of mere local history of a defunct institution.

E. K.

Malignant Disease of the Female Genital Tract. By Stanley Way, M.R.C.O.G., Gynecologist to Newcastle Regional Cancer Organiz.; Assoc. Surg., Royal Victoria Infirmary. Pp. 279; 38 ills. Phila.: Blakiston, 1951.

In this monograph the malignant tumors involving the female pelvis are concisely but thoroughly reviewed. Each lesion is considered separately and is completely discussed. Methods of diagnosis and treatment are presented in detail and an evaluation of the effectiveness of the various procedures is made. A special section on radiotherapeutics outlines dosage calculation and the nature and tissue effects of radiation in addition to the usual clinical aspects. Another portion on malignancy during pregnancy includes a discussion of all types of malignancy in the pregnant patient.

The book is well written and easily read. It is fairly well illustrated, the photomicrographs being particularly fine. It presents an excellent analysis of the current status of control of pelvic cancer by an individual of great experience, and if the advice given were heeded the general results would be greatly improved. J. W.

Medical Clinics of North America. Nationwide Number. Pp. 299-628. Philadelphia: W. B. Saunders, March, 1951. Price, $15.00 a year.

The first half of this volume is devoted to a symposium on diseases of the skin with Dr. Paul A. O'Leary as Consulting Editor. It is intended to present to the physician in general practice and to the dermatologist the present-day concepts and new methods of treatment of a few of the common skin lesions that are not of a serious nature but are frequently misinterpreted and mistreated; to evaluate the antibiotics and antihistamines in the treatment of cutaneous lesions; and to present the most recent advances in the management of several diseases which have significant systemic manifestations. This is successfully accomplished by a group of outstanding dermatologists.

The second half of the volume is a symposium in honor of William S. McCann and contains 11 articles on a wide variety of subjects in the field of Internal Medicine.

T. D.

NEW EDITIONS

Radioactive Tracers in Biology. By MARTIN D. KAMEN, Assoc. Prof. of Radiochem., Ed. Mallinckrodt Inst. of Radiol., Washington Univ. Med. Sch., St. Louis. 2nd ed. Pp. 429; ills. New York: Academic Press, 1951. Price, $7.50.

THE first edition of this terse volume on tracer methodology has met with justifiably wide acceptance. No major changes have been made in the 2nd edition, although the first portion of the book dealing with physical aspects of radioactivity and its measurement has been generally rewritten. An attempt has been made to bring up to date the applications of tracers in biology and medicine.

This book is not for the uninitiated worker. The 1st 4 chapters consist of an excellent review of the physical aspects of radioactivity and its measurement and radiation hazards, but it presupposes at least some familiarity with the elements of nuclear physics and the associated mathematics. The novice would do well to use this book in conjunction with a more elementary and detailed discussion of the essentials of nuclear physics and radioactivity.

The 2nd chapter contains an unusually lucid discussion of the properties and absorption characteristics of beta and gamma rays. The 3rd chapter deals with the theory, properties, and construction of counters. Geometry and counting efficiency are well discussed, and emphasis is placed on the importance of counting statistics.

Of special merit is the discussion, both in the text and in the appendix, on standardization of beta emitters. The appendix contains the National Bureau of Standards method of beta ray standardization in the most complete form to be found in a textbook.

The remainder of the book deals with specific isotopes and their applications in biology and constitutes an unusually complete and detailed survey of what has been done in these fields. Of more importance than the specific references to past applications and accomplishments is the presentation, in the course of discussion of the specific isotopic tracers, of the philosophy of tracer methodology in general.

The book is indispensable for all workers in the radioactive tracers. R. R.

Cleft Palate and Speech. By MURIEL E. MORLEY, B.Sc., F.C.S.T., Speech Therapist, Newcastle Gen. Hosp., Newcastle-upon Tyne, 2nd ed. Pp. 160; 56 ills. Baltimore: Williams & Wilkins, 1951. Price, $3.00.

THE evaluation of techniques of surgical repair of cleft palate, the utilization of mechanical devices, the history and development of present day procedures, and finally the needs for and the methods of speech training are helpfully included in this small book.

Typical speech defects in cleft palate permit of the following classifications: Patients in the 1st group use normal relations of tongue, lips, and teeth for the production of all sounds, but gross nasal escape results in weak consonants and nasalized vowels. In the 2nd group some consonants may be produced in normal positions but will be weak. In the 3rd group the speech consists of vowel sounds and nasal resonants only. No attempt is made to produce other consonant sounds, and speech is, of course, unintelligible.

From the earliest records of repair in 1817, through the contributions of Lane and the American surgeons, Brophy, Davis, and Dorrance, the procedues have fortunately progressed with regard to the integrity of speech. And where supplementary speech therapy is indicated (almost always necessary) Miss Morley's book provides theoretical as well as practical direction and guidance. This volume should prove an asset to the surgeon's library and fill a need for the speech pathologist. Y. N.

Textbook of X-Ray Diagnosis by British Authors. Edited by S. COCHRANE SHANKS. Vol. 2, *The Cardiovascular and Respiratory System.* By PETER KERLEY and the late EDWARD WING TWINING. 2nd ed. Pp. 702; 605 ills. Phila.: W. B. Saunders, 1951. Price, $15.00.

A considerable number of illustrations has been added to this 2nd edition of a work that is one of the very few complete English texts of diagnostic radiology. The section on the respiratory tract is excellent. A point emphasized (although neglected in many busy American roentgen departments) is that fluoroscopy and film studies of the chest are both essential and complementary methods in the complete roentgen examination of the chest. It is strange to find detailed instructions still included for the use of fluroscopy at the bedside in the home. The informative discussion of pneumoconiosis draws on the extensive experience that British roentgenologists have in this field.

The section on congenital heart disease is somewhat disappointing since the new developments in cardiac surgery and angiocardiography have been omitted. H. S.

Micro-Analysis in Medical Biochemistry. By E. J. KING, Ph.D., Prof. Chem. Path., Univ. of London Postgrad. Med. School. 2nd ed. Pp. 222; 22 ills. New York: Grune & Stratton, 1951. Price, $3.50.

THIS compact manual of methods for routine biochemical and research analyses has added procedures for the determination of ketosteroids, formaldehyde-stable acid phosphates, effective renal plasma flow and glomerular filtration rate, fat balance, and other new analytical methods. The descriptions for colorimetric procedures are given both for photoelectric instruments and for the Duboscq type of colorimeter. An added convenience to British workers is the inclusion of references to firms from which necessary supplies may be obtained. C. Z.